Paid Circulation, 32,636

The New England Journal of Medicine

FORMERLY THE BOSTON MEDICAL AND SURGICAL JOURNAL — *Established 1828*

VOLUME 252 MARCH 3, 1955 NUMBER 9

Original Articles

Pathologic Changes Associated with the Use of Sodium Ethylene Diamine Tetra-Acetate in the Treatment of Hypercalcemia: Report of Two Cases with Autopsy Findings 331
H. R. Dudley, A. C. Ritchie, A. Schilling and W. H. Baker

Successful Calcium Disodium Ethylene Diamine Tetra-Acetate Treatment of Lead Poisoning in an Infant 338
Leighton A. Kneller, Henry S. M. Uhl and Jacob Brem

Ureterolleostomy, An Efficacious Method of Urinary Diversion: Report of Six Cases . 341
George R. Read and Alfred Hurwitz

Special Article

Love: A Clinical Definition 345
Philip Solomon

Massachusetts Medical Society 369
Massachusetts Department of Public Health . . 369

Medical Progress

Syphilis (Concluded) 351
Robert F. Tilley

Medical Intelligence

Doctors Afield: Francis Brett Young . . . 357
John Lister

Case Records of the Massachusetts General Hospital . . 358

Editorials

Chelating Agents 367
Sturm und Drang 368
Vanishing Sex 368
Amo, Amas 368
Catastrophes of 1954 369

Correspondence 370
Notices 371

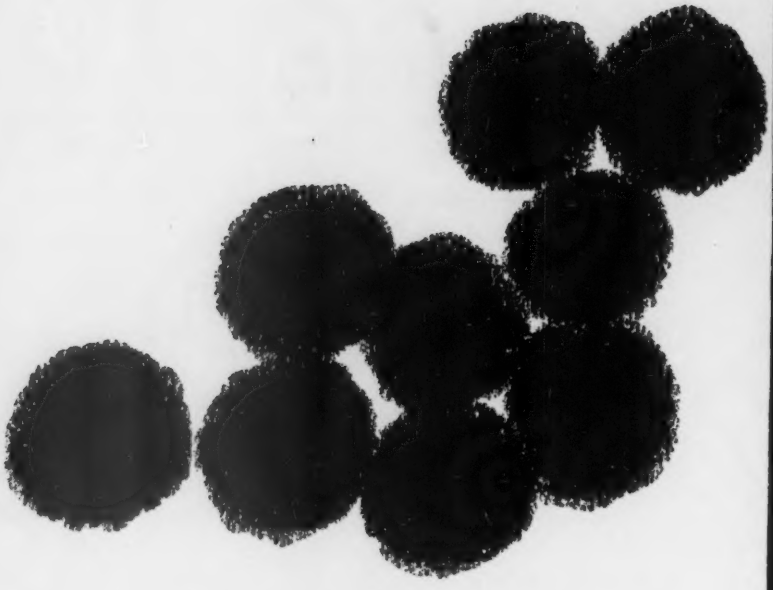
A nationwide symposium on the Rheumatic Diseases

The Medical Clinics of North America

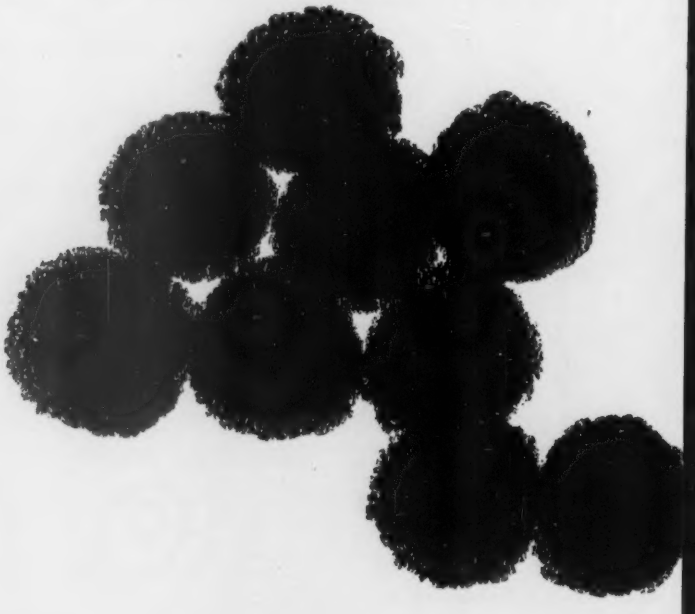
In the *March* Number of this "postgraduate course in medicine," leading internists from all over the United States discuss various aspects of the *Rheumatic Diseases.* Included are nineteen articles, all new and extremely practical, on such topics as: Protean Manifestations of the Connective Tissue Diseases; Recent Advances in Diagnosis and Treatment of Rheumatic Fever; Clinical Manifestations of Rheumatoid Arthritis; Basic Treatment in Rheumatoid Arthritis; Cortisone, ACTH and Phenylbutazone in Long-Term Therapy of Rheumatoid Arthritis; Psychiatric Considerations in Rheumatoid Arthritis; Hereditary Factors in Arthritis; and Painful Shoulder Syndromes: Their Diagnosis and Treatment.

By leading internists. Issued serially, every other month, one illustrated volume of about 300 pages, 6" x 9". Per year (six numbers): Cloth, $18.00; Paper, $15.00. Sold only by a year of six consecutive numbers.

W. B. Saunders COMPANY
WEST WASHINGTON SQUARE, PHILADELPHIA 5



to combat resistant bacteria...



Chloromycetin®

The rising incidence of bacterial resistance to various antibiotics constitutes a serious therapeutic problem. Many infections, once readily controlled, are now proving difficult to combat. Administration of CHLOROMYCETIN (chloramphenicol, Parke-Davis) is often useful in these cases because this notable, broad-spectrum antibiotic is frequently effective where other antibiotics fail.

"...An advantage of CHLOROMYCETIN appears to be its relatively low tendency to induce sensitization in the host or resistance among potential pathogens under clinical conditions."*

CHLOROMYCETIN is a potent therapeutic agent and, because certain blood dyscrasias have been associated with its administration, it should not be used indiscriminately or for minor infections. Furthermore, as with certain other drugs, adequate blood studies should be made when the patient requires prolonged or intermittent therapy.

*Pratt, R., & Dufrenoy, J.: Texas Rep. Biol. & Med. *12*:145, 1954.

PARKE, DAVIS & COMPANY • DETROIT 32, MICHIGAN

MASSACHUSETTS MEDICAL SOCIETY

1954-1955

OFFICERS AND STANDING COMMITTEES

President
Curtis C. Tripp, New Bedford

President-Elect
Conrad Wesselhoeft, Boston

Vice-President
Samuel A. Dibbins, Lowell

Secretary
Robert W. Buck, Waban

Treasurer
Eliot Hubbard, Jr., Cambridge

Assistant Treasurer
Norman A. Welch, West Roxbury

Orator
Carl Bearse, Cambridge

Delegates to the American Medical Association
Harold R. Kurth, Lawrence; Earle M. Chapman, Boston; Norman A. Welch, West Roxbury; Lawrence R. Dame, Greenfield; Philip S. Foisie, Boston; Charles G. Hayden, West Newton.

Executive Secretary
Robert St. B. Boyd, Boston

Executive Offices, 22 Fenway, Boston 15, Telephone KE 6-8812

Committee on Publications
Chairman, Richard M. Smith; Oliver Cope, James P. O'Hare, Richard E. Alt, James M. Faulkner.

Committee on Arrangements
Chairman, Arthur S. Pier, Jr.; Archie A. Abrams, H. Thomas Ballantine, Jr., J. Gordon Scannell, Thomas B. Quigley.

Committee on Ethics and Discipline
Chairman, Frederic Hagler; Joseph C. Merriam, Milton J. Quinn, Allen S. Johnson, Horatio Rogers.

Committee on Medical Education
Chairman, Robert P. McCombs; James M. Faulkner, Robert T. Monroe, Joseph M. Hayman, Jr., George P. Berry.

Committee on Membership
Chairman, Lewis S. Pilcher; Henry F. Howe, Donald Munro, Samuel N. Vose, Stuart N. Gardner.

Committee on Public Health
Chairman, Archie A. Abrams; Hugh R. Leavell, Robert D. Cox, James E. Vance, Paul J. Jakmauh.

Committee on Medical Defense
Chairman, Charles B. Burbank; Horatio Rogers, Lee G. Kendall, Philip LeCompte, Carl Bearse.

Committee on Finance
Chairman, Charles G. Shedd; Henry H. Faxon, Francis C. Hall, Lyman H. Hoyt, John W. Norcross.

Committee on Society Headquarters
Chairman, Albert A. Hornor; Walter G. Phippen, Joseph S. Barr, Dwight O'Hara, Joseph Garland.

Committee on Industrial Health
Chairman, George F. Wilkins; Henry C. Marble, Karl T. Benedict, Harriet L. Hardy, George E. Morris, Albert O. Seeler, Robert B. O'Connor, Daniel L. Lynch (advisory member).

Committee on Benevolence
Chairman, Dwight O'Hara; Theodore L. Badger, Robert W. Buck, Eliot Hubbard, Jr., Charles C. Lund.

Committee on By-Laws and Council Rules
Chairman, Albert A. Hornor; Donald Munro, Carl Bearse, William E. Murphy, Fabyan Packard.

OFFICERS OF THE SECTIONS

Medicine
Chairman, Arthur S. Pier, Jr., Boston; *vice-chairman*, Ralph H. Wells, Lexington; *secretary*, Harold F. Brown, Newton Centre.

Physical Medicine
Chairman, Fritz Friedland, Boston; *secretary*, William J. Shriber, Boston.

Dermatology
Chairman, Salvatore J. Messina, Newton Centre; *secretary*, William R. Hill, Jr., Belmont.

Radiology
Chairman, Robert E. Grandfield, Boston; *secretary*, Martin H. Wittenborg, Boston.

Obstetrics & Gynecology
Chairman, John R. Barker, Needham; *vice-chairman*, Smith G. Philips, Worcester; *secretary*, Archie A. Abrams, Brookline.

Industrial Health
Chairman, Karl T. Benedict, West Boylston; *secretary*, Thomas P. Kendrick, Brookline.

Psychiatry and Neurology
Chairman, Harry C. Solomon, Jamaica Plain; *secretary*, Bardwell H. Flower, Worcester.

Surgery
Chairman, Chester Howe, Jamaica Plain; *secretary*, Frederick P. Ross, Fitchburg; executive committee — Frederick P. Ross, Douglas A. Farmer, William W. Babson.

Pediatrics
Chairman, Fred H. Allen, Holyoke; *secretary*, Harry L. Mueller, Winchester.

Physiology and Pathology
Chairman, David Skinner, West Newton; *vice-chairman*, John D. Houghton, Newton Centre; *secretary*, Harry G. Olken, Lynn.

Anesthesiology
Chairman, M. Gene Black, Holyoke; *secretary*, Bernard D. Briggs, Stoneham.

Ophthalmology and Otolaryngology
Chairman, Brendan D. Leahey, Lowell; *vice-chairman*, Edgar M. Holmes, Auburndale; *secretary*, John E. McKeigue, Cambridge.

OFFICERS OF THE DISTRICT MEDICAL SOCIETIES

BARNSTABLE — *President*, Sheldon L. Hunt, Yarmouthport; *vice-president*, Hermon Howes, South Yarmouth; *secretary*, Lee Britton, South Yarmouth; *treasurer*, John O. Niles, Osterville.

BERKSHIRE — *President*, Edward T. Forsley, Pittsfield; *vice-president*, Helen Scoville, Pittsfield; *secretary*, Daniel N. Beers, Pittsfield; *treasurer*, Theodore W. Jones, Pittsfield.

BRISTOL NORTH — *President*, Milton E. Johnson, Attleboro; *vice-president*, Joseph E. Nunes, Taunton; *secretary*, J. Allen Bryer, Jr., North Attleboro; *treasurer*, Charles E. Hoye, Jr., Taunton.

BRISTOL SOUTH — *President*, William Rosen, New Bedford; *vice-president*, Daniel F. Gallery, Fall River; *secretary* and *treasurer*, James E. Fell, Fall River.

CHARLES RIVER — *President*, Gerald Garcelon, West Newton; *vice-president*, Kenneth Christophe, Needham; *secretary*, Knowles B. Lawrence, Needham; *treasurer*, Henry Godfrey, Auburndale.

ESSEX NORTH — *President*, Adolph A. De Nuccio, Lawrence; *vice-president*, Philip W. Blake, Andover; *secretary*, David W. Wallwork, North Andover; *treasurer*, James F. Seccareccio, Lawrence.

ESSEX SOUTH — *President*, Charles A. Palladino, Lynn; *vice-president*, Robert T. Moulton, Salem; *secretary*, Ever Curtis, Gloucester; *treasurer*, Andrew Nichols, III, Hathorne.

FRANKLIN — *President*, Milton M. Sisson, Greenfield; *vice-president*, Warren D. Thomas, Turners Falls; *secretary* and *treasurer*, Emid D. Elgosin, Millers Falls.

HAMPDEN — *President*, Laurence A. Putnam, Holyoke; *vice-president*, Joseph P. Derby, Springfield; *secretary*, Allen G. Rice, Springfield; *treasurer*, Howard B. Brown, Springfield.

HAMPSHIRE — *President*, Stephen Brown, Amherst; *vice-president*, David B. Jennison, Northampton; *secretary*, Gordon D. Arnold, Northampton; *treasurer*, Joseph R. Hobbs, Williamsburg.

MIDDLESEX EAST — *President*, Robert Dutton, Wakefield; *vice-president*, John C. Anderson, Stoneham; *secretary*, William F. Hickey, Jr., Winchester; *treasurer*, Charles W. DeWolf, Melrose.

MIDDLESEX NORTH — *President*, Leonard Dursthoff, Lowell; *vice-president*, Philip G. Berman, Lowell; *secretary*, Germain Bouchard, Lowell; *treasurer*, Mona Mehan, Lowell.

MIDDLESEX SOUTH — *President*, Alexander A. Levi, Boston; *vice-president*, Ralph H. Wells, Lexington; *secretary*, David C. Dow, Jr., Cambridge; *treasurer*, Fabyan Packard, Winchester.

MIDDLESEX WEST — *President*, Nicholas A. Mastroianni, Milford; *vice-president*, Maurice E. Costin, Framingham; *secretary*, John P. Ahearn, Marlboro; *treasurer*, Nicholas J. Capece, Milford.

NORFOLK — *President*, Basil E. Barton, West Roxbury; *vice-president*, Urban H. Eversole, Wellesley; *secretary*, Solomon L. Skvirsky; *treasurer*, David L. Lionberger, Boston.

NORFOLK SOUTH — *President*, Ebenezer K. Jenkins, South Braintree; *vice-president*, Arthur Rappeport, Quincy; *secretary*, Joseph P. Leone, Quincy; *treasurer*, Burton F. Elder, Hingham.

PLYMOUTH — *President*, John C. Angley, Bryantville; *vice-president*, Donald A. Martin, South Hanson; *secretary*, Samuel Gale, Brockton; *treasurer*, Ernest E. Wiesner, Brockton.

SUFFOLK — *President*, Earle M. Chapman, Boston; *vice-president*, William E. Browne, Boston; *secretary*, Charles G. Shedd, Brookline; *treasurer*, Carl F. Maraldi, Boston.

WORCESTER — *President*, Edward J. Crane, Holden; *vice-president*, John W. O'Meara, Worcester; *secretary*, Burte Guterman, Worcester; *treasurer*, Arthur D. Ward, Worcester.

WORCESTER NORTH — *President*, James G. Simmons, Fitchburg; *vice-president*, Philip F. Hilton, Leominster; *secretary*, Seymour I. Nathanson, Fitchburg; *treasurer*, Frederick H. Thompson, Jr., Fitchburg.

Entered as second-class matter, November 16, 1932, at the post office at Boston, Massachusetts, under the Act of March 3, 1879. Published weekly at 8 Fenway, Boston 15. Domestic, $8.00 per year.

ELECTRON PHOTOMICROGRAPH

Streptococcus pyogenes 36,000 X

Streptococcus pyogenes is a Gram-positive organism commonly involved in a great variety of pathologic conditions, including

scarlet fever • tonsillitis • pharyngitis • otitis media • sinusitis
bronchopulmonary disease • pyoderma • empyema • septicemia • meningitis
mastoiditis • vaginitis • rheumatic fever • acute glomerulonephritis

It is another of the more than 30 organisms susceptible to

PANMYCIN* HCl

100 mg. and 250 mg. capsules
125 mg./tsp. and 250 mg./tsp. oral suspension (Panmycin Readimixed)

Upjohn

*TRADEMARK, REG. U. S. PAT. OFF.

Cortril® tablets

(brand of hydrocortisone)

the predominant anti-rheumatic hormone, "...highly effective in suppressing the activity of the disease and... maintaining control of rheumatic manifestations."[1] Side actions are "fewer and less pronounced."[2]

supplied: scored tablets, 10 mg. and 20 mg.

also available: CORTRIL Topical Ointment

CORTRIL Acetate Aqueous Suspension for intra-articular injection

CORTRIL Acetate Ophthalmic Ointment

TERRA-CORTRIL* Ophthalmic Suspension

TERRA-CORTRIL Topical Ointment

New easier-to-write, easier-to-remember names

Pfizer PFIZER LABORATORIES, *Brooklyn 6, New York*
Division, Chas. Pfizer & Co., Inc.

references: 1. Boland, E. W., and Headley, N. E.: J.A.M.A. 148:981, March 22, 1952. 2. Boland, E. W.: M. Clin. North America. Philadelphia and London, W. B. Saunders Company, March, 1954, p. 337.

*brand of oxytetracycline and hydrocortisone

MAXIMUM SAFE ANALGESIA

(free from risk of addiction)

in whatever potency each patient may require

By facilitating the optimal analgesic medication of each patient without risk of addiction, PHENAPHEN and PHENAPHEN WITH CODEINE have proven their wide range of clinical usefulness — for cases of simple headache to many of late cancer.

True pharmacodynamic synergism enhances the therapeutic potency of each of the 4 forms available for discriminating prescription:

PHENAPHEN
— basic non-narcotic formula
Each brown and white capsule contains:
Acetylsalicylic acid (2½ gr.).....162 mg.
Phenacetin (3 gr.).....194 mg.
Phenobarbital (¼ gr.).....16.2 mg.
Hyoscyamine sulfate ($\frac{1}{2000}$ gr.)..0.031 mg.

Phenaphen No. 2
PHENAPHEN
with CODEINE PHOSPHATE ¼ GR.
Each black and yellow capsule contains:
The basic phenaphen formula plus
Codeine phosphate (¼ gr.).....16.2 mg.

Phenaphen No. 3
PHENAPHEN
with CODEINE PHOSPHATE ½ GR.
Each black and green capsule contains:
The basic phenaphen formula plus
Codeine phosphate (½ gr.).....32.4 mg.

Phenaphen No. 4
PHENAPHEN
with CODEINE PHOSPHATE 1 GR.
Each green and white capsule contains:
The basic phenaphen formula plus
Codeine phosphate (1 gr.).....64.8 mg.

A. H. ROBINS CO., INC. • Richmond 20, Virginia

Ethical Pharmaceuticals of Merit since 1878

Phenaphen® Robins

Phenaphen® with Codeine

BLUE
AT
BREAKFAST?

STOP morning sickness
with
BONADOXIN*
(BRAND OF MECLIZINE HCl, PYRIDOXINE HCl)

RESULTS
of
this
new
COMBINATION

In 50 patients with nausea and vomiting, Weinberg reports 88% good to excellent results.[1]

In another series, Bonadoxin abolished vomiting in 40 of 41 gravida, eliminated nausea in 30 of the 41.[2]

Each Bonadoxin tablet contains:

Meclizine HCl . . . . 25 mg.
Pyridoxine HCl . . . 50 mg.

Mild cases: One Bonadoxin tablet at bedtime.

Severe cases: One at bedtime and on arising.

In bottles of 25, prescription only.

1. Weinberg, Arthur, and Werner, W. E. E: Benadoxin, a New Effective Oral Therapy for Hyperemesis Gravidarum, New York Medical College and Rockaway Beach Hospital, 1954.
2. Personal communication.

ROERIG Rx CHICAGO 11, ILLINOIS

*TRADEMARK

broad spectrum antibiotic of choice

promptly reaches high levels in the urine

crosses the intact meningeal barrier more readily than the other broad spectrum antibiotics

produces higher blood levels than the other broad spectrum antibiotics

less gastrointestinal side effects than the other broad spectrum antibiotics

Minimum adult dose: **250 mg. q.i.d.**
250 mg. capsules, bottles of 16 and 100.
50 and 100 mg. capsules, bottles of 25 and 100.

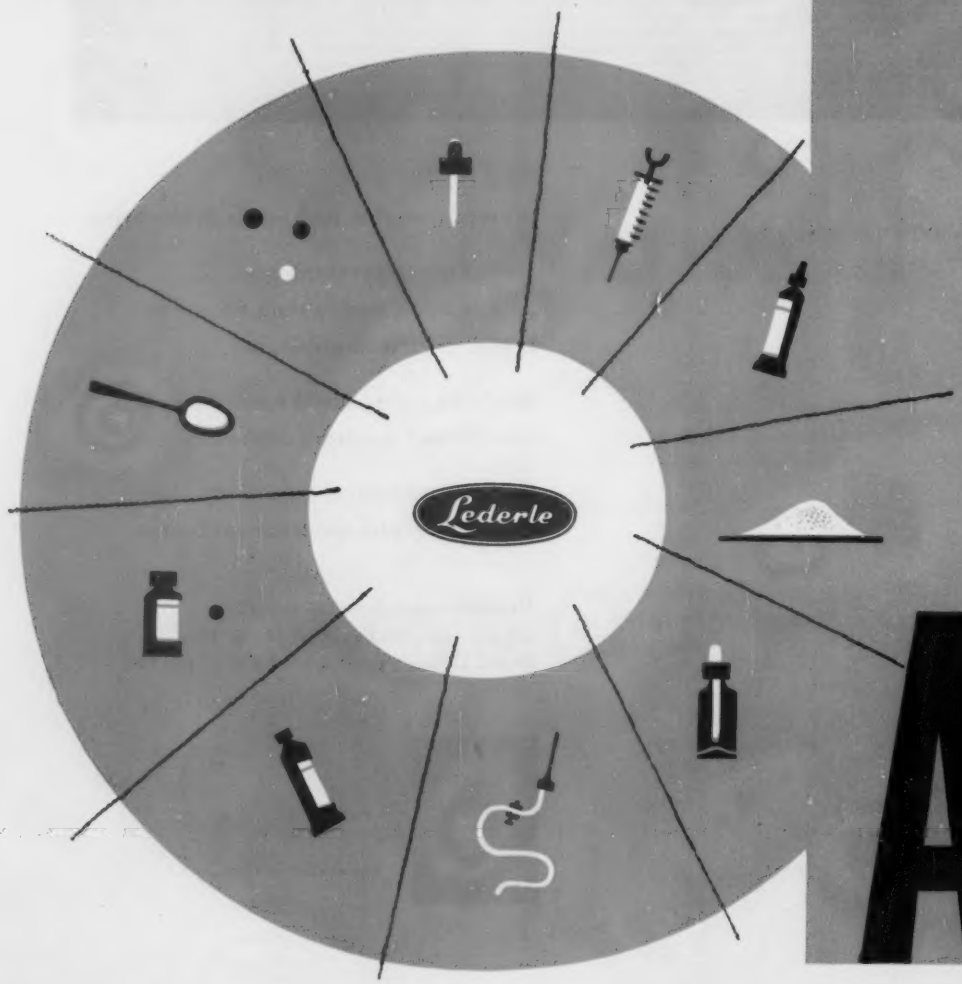
SQUIBB

"STECLIN" IS A SQUIBB TRADEMARK

ACHROMYCIN CAPSULES

The most widely prescribed form
of this widely prescribed antibiotic.
ACHROMYCIN Capsules are available in potencies
of 50 mg., 100 mg., and 250 mg.

for every need—a suitable dosage form



AC

*REG. U.S. PAT. OFF.

Other Dosage Forms:

TABLETS: 50, 100, and 250 mg.

PEDIATRIC DROPS (Cherry Flavor): 100 mg. per cc. (approx. 5 mg. per drop), 10 cc. bottle

ORAL SUSPENSION (Cherry Flavor): 250 mg. per teaspoonful (5 cc.), 1 oz. bottle

SPERSOIDS* Dispersible Powder (Chocolate Flavor): 50 mg. per rounded teaspoonful (3 Gm.), 12 and 25 dose bottle

SOLUBLE TABLETS: 50 mg.

INTRAVENOUS: vials of 100, 250, and 500 mg.

INTRAMUSCULAR: vial of 100 mg.

OINTMENT (3%): ½ and 1 oz. tubes

OPHTHALMIC OINTMENT (1%): ⅛ oz. tube

OPHTHALMIC SOLUTION: vial of 25 mg. with sterilized dropper vial

EAR SOLUTION (0.5%): 10 cc. dropper bottle

SYRUP (Cherry Flavor): 125 mg. per teaspoonful (5 cc.), 2 oz. bottle

In any of its numerous dosage forms, ACHROMYCIN is a potent weapon to combat a variety of infections. This true broad-spectrum antibiotic has proved effective in controlling Gram-negative and Gram-positive bacteria, rickettsia, spirochetes, and certain viruses and protozoa.

And ACHROMYCIN is unusually kind to the patient! Extensive use, in children and adults, has shown it to be practically free of untoward side reactions. ACHROMYCIN diffuses rapidly in body tissues and fluids, is readily soluble, and remains stable for 24 hours in solution.

When a broad-spectrum antibiotic is indicated, remember—for your convenience, for the patient's comfort, there's a particular dosage form of ACHROMYCIN to fill the need!

LEDERLE LABORATORIES DIVISION *AMERICAN Cyanamid COMPANY* PEARL RIVER, NEW YORK

Now available as Syrup—ready-mixed!

ACHROMYCIN*

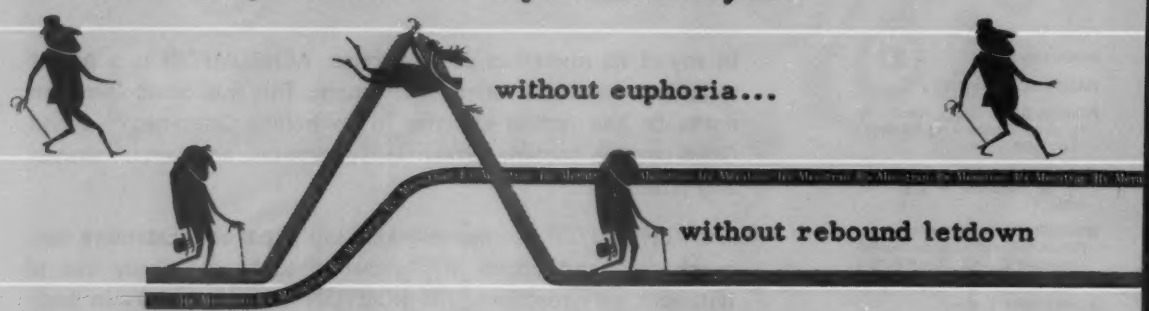
TETRACYCLINE LEDERLE

NEW DRUG

Meratran

(pipradrol hydrochloride)

a unique central motivant with demonstrated subcortical activity subtly returns your emotionally fatigued and depressed patients to their usual level of alertness, interest and productivity[1-2]...



Meratran's action, in easily adjusted doses, is prompt—subtle—comfortable—Its effectiveness is prolonged.

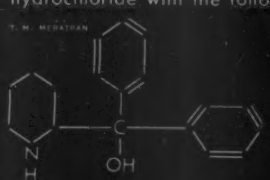
• no appreciable effect on blood pressure and respiration • restores needed sense of well-being • no tolerance or drug habituation • normal appetite undisturbed • no jitters - no apprehension • little or no insomnia • wide range of safety • no rebound letdown

Rx INFORMATION

Meratran

Indications: Emotional fatigue, unhappiness of more common type (financial worry, social stress). Situational stress or *mild* depression. Adjunctive therapy in certain psychoses and psychoneuroses.[3,4]

Composition: alpha-(2-piperidyl) benzhydrol hydrochloride with the following structure:



Dosage: For emotional fatigue and mild depression, *1 to 6 mg. daily. Individual patient response must be observed and daily dosage and duration of administration adjusted* to patient response.

Supplied: Small pink tablets containing: 1 mg. Meratran (pipradrol) hydrochloride.* Bottles of 100.

*Alpha-(2-piperidyl) benzhydrol hydrochloride.

1. Heath, R. C.: Discussion of paper by Howard D. Fabing (alpha-[2-piperidyl] benzhydrol hydrochloride, a new central stimulant in the treatment of blepharospasm, spasmodic torticollis and narcolepsy) presented before the American Neurological Association, Atlantic City, June 14, 1954. 2. Fabing, H. D., Hawkins, J. R., Moulton, J. A. L.: Clinical studies on alpha-(2-piperidyl) benzhydrol hydrochloride, a new antidepressant drug. Presented before the American Psychiatric Association, St. Louis, Missouri, May 3, 1954. 3. Fabing, H. D.: Alpha-(2-piperidyl) benzhydrol hydrochloride, a new central stimulant, in the treatment of blepharospasm, spasmodic torticollis and narcolepsy, preliminary report (Motion Picture Demonstration). American Neurological Association, June 14, 1954. 4. Himwich, H. E.: Discussion of paper (reference 2), American Psychiatric Association, May 3, 1954.

Merrell Since 1828

THE WM. S. MERRELL COMPANY

New York • CINCINNATI • St. Thomas, Ontario

PIONEER IN MEDICINE FOR OVER 125 YEARS

A Summary of Recent Research*

Wine in Modern Medical Practice

"...in response to the demand within the medical profession that the true values or deficiencies of wine be ascertained, that there be a clear separation of fact from folklore, and that there be an impartial analysis and study of those features which can be scientifically measured...."*

a series of independently conducted research programs has been in progress for many years under the sponsorship of the Wine Advisory Board of California.

Some of the most important new research findings have been incorporated in a small brochure* specifically written for the medical profession. The booklet considers the role of wine in the treatment of the convalescent and the geriatric patient, as well as its use in the specialized fields of gastroenterology, cardiology, urology, etc. There is mention, too, of the psychobiologic effects of wine, such as its capacity to add a touch of interest and "elegance" to restricted or special dietaries.

A copy* is available to you, at no expense, by writing to:

Wine Advisory Board, 717 Market Street, San Francisco 3, California.

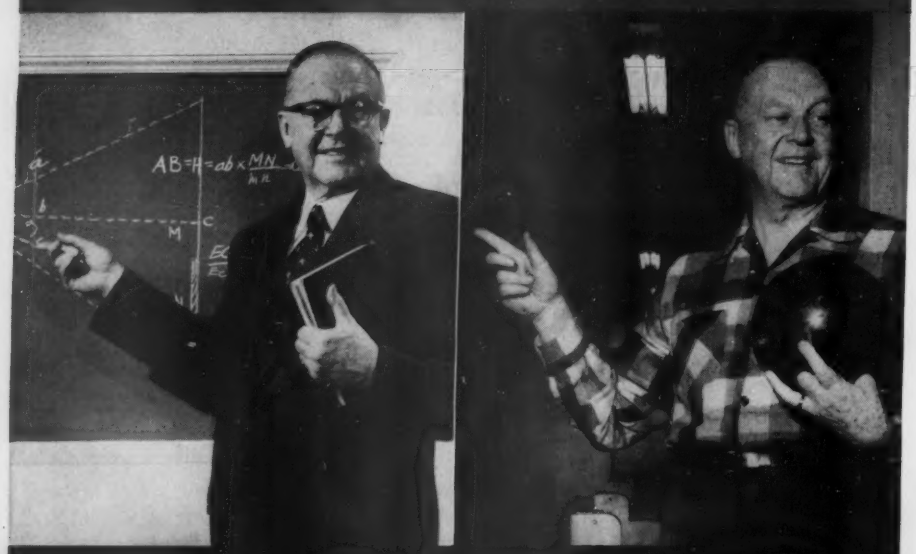
*"Uses of Wine in Medical Practice"

Pyridium®

(PHENYLAZO-DIAMINO-PYRIDINE HCl)

Gratifying relief from urogenital discomforts *in a matter of minutes*

KEY ADVANTAGES: Rapid-acting, nontoxic urinary analgesic. No systemic effects. Compatible with sulfonamides and antibiotics.



FOR COMFORT
ON THE JOB . . . AND AT PLAY

EFFECTIVE—In a study of 118 cases of pyelonephritis, cystitis, prostatitis and urethritis,[1] PYRIDIUM relieved or abolished dysuria in 95% of the patients and greatly reduced or abolished frequency in 85% of the cases.

NONTOXIC—PYRIDIUM produces rapid and entirely local analgesia of the urogenital mucosa. It may be administered in conjunction with sulfonamides or antibiotics to relieve distressing urogenital symptoms in the interval before the antibacterials can act.

PHYSIOLOGICAL—The soothing analgesic action of PYRIDIUM promotes relaxation of the sphincter mechanism of the bladder. This relaxation helps the patient to overcome urinary retention of spastic origin.

PSYCHOLOGICAL—PYRIDIUM imparts a characteristic orange-red color to the urine. This color-change gives patients added assurance of prompt action of the drug.

SUPPLIED: In 0.1 Gm. (1½ gr.) tablets, vials of 12 and bottles of 50, 500, and 1,000.

PYRIDIUM is the registered trade-mark of Nepera Chemical Co., Inc., for its brand of phenylazo-diamino-pyridine HCl. Sharp & Dohme, Division of Merck & Co., Inc., sole distributor in the United States.

SHARP & DOHME
PHILADELPHIA 1, PA.
DIVISION OF MERCK & CO., INC.

REFERENCE: 1. Kirwin, T. J., Lowsley, O. S., and Menning, J., Am. J. Surg. **62**:330-335, December 1943.

When the mother asks—

"Which vitamin drops should I use?" --
she looks to you for specific advice.
And when you specify easy-to-take
Vi-Penta® Drops 'Roche,' you know
they are dated to ensure full
potency...they contain synthetic
vitamin A plus seven other vitamins
(including B_6)...and they taste good.

Especially for pediatric infectious —

When you prescribe Gantrisin®(acetyl) Pediatric Suspension 'Roche,' you may be sure of two things: It really tastes good -- so good even sick children take it gladly -- and it offers wide-spectrum antibacterial therapy that is usually well tolerated.

ELECTRON PHOTOMICROGRAPH

Escherichia coli 36,000 X

Escherichia coli ("colon bacillus") is a Gram-negative organism
commonly involved in
urinary tract infections and peritonitis,
and is an important etiologic agent of otitis media, mastoiditis, enteritis,
and septicemia in infants.

It is another of the more than 30 organisms susceptible to

PANMYCIN* HCl

TETRACYCLINE HYDROCHLORIDE

100 mg. and 250 mg. capsules
*125 mg./tsp. and 250 mg./tsp. oral suspension (***Panmycin** *Readimixed)*

Upjohn

*TRADEMARK, REG. U. S. PAT. OFF.

For assured dependability in Digitalis administration

Physiologically Standardized

Pil. Digitalis (Davies, Rose)

0.1 Gram (approx. 1½ grains)

Comprise the entire properties of the leaf.

Clinical samples sent to physicians on request.

Davies, Rose & Company, Limited — Boston 18, Massachusetts

D-25

Planning the Low-Purine Diet for a long run...

Imagination is essential to this diet since your patient may have to follow it for many years. These diet "do's" can show him how to use eggs, cheese, and milk—a trio of almost purine-free foods—to supply the major portion of his protein.

In these, the trio plays a solo—

Eggs baked in pimiento-flecked cheese sauce are hard to resist. Or, if your patient prefers, the sauce can be poured over hard-cooked eggs.

A casserole of eggplant and tomatoes layered alternately with ricotta or cottage cheese makes a satisfying entree. Add a sprinkle of grated parmesan with a fine Italian hand.

Your patient may like his eggs poached in tomato juice. Then serve them in a soup bowl with a frill of chopped parsley on top.

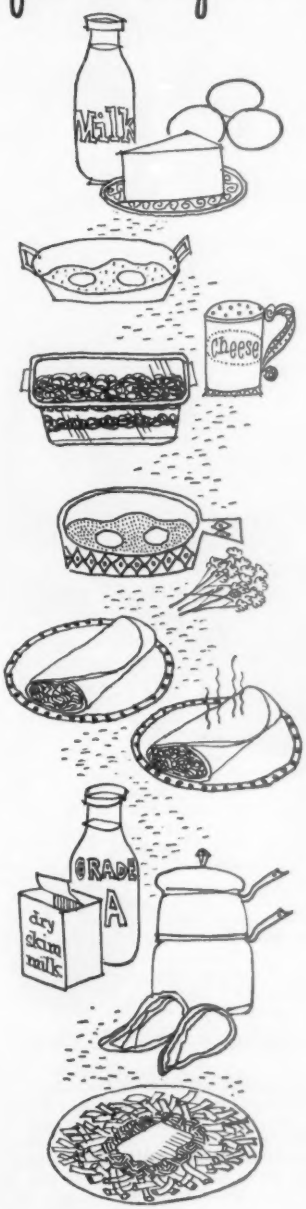
In these, the trio plays accompaniment—

Ham 'n' egg rolls come hot or cold. For hot, roll a warm slice of ham around eggs that have been scrambled with a pinch of savory. For cold, roll ham around egg salad mixed with cottage cheese.

Oyster stew can be creamy without cream when the milk is bolstered with dry skim milk powder. A pinch of thyme and some chopped parsley add savor.

Broiled salmon or tuna-burgers nestle nicely in a nest of noodles. A slice of cheese on top adds color and broils to a bubbling brown.

These suggestions are only a few of the possible combinations of this versatile trio. And the adequate protein nutrition they make possible, plus a liberal intake of fluids, may help establish a regimen that will please you both.



United States Brewers Foundation

Beer—America's Beverage of Moderation

104 calories, 17 mg. sodium/8 oz. glass (Average of American beers)

If you'd like reprints for your patients, please write United States Brewers Foundation, 535 Fifth Avenue, New York 17, N. Y.

'Sulfa-Neolin'

(BENZATHINE PENICILLIN—G WITH SULFONAMIDES, LILLY)

chocolate-mint-flavored suspension for the treatment of mixed infections caused by penicillin-susceptible and/or sulfonamide-sensitive organisms

The twofold antibacterial action of 'Sulfa-Neolin' is particularly effective in mixed infections. The combined action of penicillin and the sulfonamides is also of value in combating relatively resistant organisms. Since the mode of attack of penicillin differs from that of the sulfonamides, it is more difficult for an organism to develop resistance to the combination than to either drug used alone. The tasty chocolate-mint flavor of 'Sulfa-Neolin' quickly wins youngsters' approval.

Each 5 cc. (approximately 1 teaspoonful) contain sulfa: diazine, merazine, methazine, 0.167 Gm. each, and benzathine penicillin—G, 300,000 units. 'Sulfa-Neolin' is stable at room temperature for two years.

Dosage: Average dose is 1 teaspoonful four times a day.

Suspension 'Sulfa-Neolin' is supplied in 60-cc. bottles (M-120).

ELI LILLY AND COMPANY • INDIANAPOLIS 6, INDIANA, U.S.A.

The New England
Journal of Medicine

Copyright, 1955, by the Massachusetts Medical Society

Volume 252 MARCH 3, 1955 Number 9

PATHOLOGIC CHANGES ASSOCIATED WITH THE USE OF SODIUM ETHYLENE DIAMINE TETRA-ACETATE IN THE TREATMENT OF HYPERCALCEMIA*

Report of Two Cases with Autopsy Findings

H. R. DUDLEY, M.D.,† A. C. RITCHIE, M.B., CH.B., PH.D.,‡ A. SCHILLING, M.D.,§ AND W. H. BAKER, M.D.¶

BOSTON

RECENTLY, a new compound, sodium ethylene diamine tetra-acetate (sodium EDTA), ‖ has been used in the treatment of hypercalcemia.[1-4] This is a powerful chelating agent with a strong avidity for calcium and heavy metals. When given intravenously it exchanges its sodium ions for calcium to form a soluble chelate binding the metal in an un-ionized form. The calcium chelate so formed is rapidly and almost completely excreted by the kidneys, carrying with it the bound calcium.[5-7] Because of the paucity of reports of toxic reactions to the drug, 2 cases of hypercalcemia treated by intravenous administration of large doses of sodium EDTA are here recorded. In each, in addition to the lesions expected, there were three unexpected pathological findings: the renal tubules, especially the proximal convoluted tubules, were severely damaged; the reticuloendothelial cells were enlarged and contained coarse eosinophilic granules; and internal hemorrhages were extensive.

CASE REPORTS

CASE 1. M.F. (M.G.H. 828566), a 30-year-old married woman, was admitted to the hospital on November 25, 1953. Three years previously a radical mastectomy on the right side had been performed for adenocarcinoma of the breast. This operation was shortly followed by a hysterectomy and bilateral salpingo-oöphorectomy. She was perfectly well for 2½ years, but in August, 1953, began to experience intermittent pain in the lower back. X-ray studies in September were reported as negative, but repeated examination in October revealed the collapse of the 2d lumbar vertebra; x-ray therapy was begun to this area. A repeat metastatic series on November 3 demonstrated widespread osteolytic lesions in the skull, ribs, spine and pelvis. Examination of the blood at that time showed a serum calcium of 10.6 mg. and a serum phosphorus of 6.65 per 100 cc., with an alkaline phosphatase of 4.35 Bodansky units. A total tumor dose of 1000 r was delivered to the lower back, with some relief of pain. One week before her last admission she again experienced severe pain in the lower back and was given testosterone propionate, 50 mg. intramuscularly, every other day. After the 2d dose she became drowsy and polydipsia, polyuria and dryness of the mouth developed. Because of these symptoms she was admitted to the hospital, and testosterone therapy was discontinued.

Physical examination revealed an acutely and chronically ill, dehydrated woman complaining of diffuse tenderness over the spine, scapula and right 2d and 3d ribs anteriorly. Deep tendon reflexes were markedly hypoactive, but equal. A metastatic x-ray series on November 27 showed considerable progression of osteolytic disease throughout the skeletal system. The serum calcium was 16.0 mg., serum phosphorus 3.9 mg., alkaline phosphatase 3.2 Bodansky units, and nonprotein nitrogen 40 mg. per 100 cc.; the sodium was 138 milliequiv., potassium 4.4 milliequiv., and chloride 94 milliequiv. per liter. The hemoglobin was 9.7 gm. per 100 cc., and urinalysis revealed a ++ test for albumin, with occasional granular and hyaline casts in the sediment.

During the 1st hospital week 2.5 per cent sodium citrate was administered daily, without effect on the serum calcium levels. On the 8th hospital day sodium EDTA was begun, the daily dose being given intravenously in dextrose and water. The 1st dose was 5 gm. (90 mg. per kilogram of body weight) in a 4-hour period. The serum calcium, as measured by the EDTA and oxalate precipitation methods, fell rapidly, from 15.2 mg. per 100 cc. at the outset to 14.4 mg. after ½ hour, 13.6 mg. after 2 hours and 12.8 mg. after 3 and 4 hours, when the intravenous infusion was discontinued. After 12 hours the serum calcium had risen again to 13.6 mg. per 100 cc. There was little clinical change, though the deep tendon reflexes had returned to normal.

On the 9th hospital day 6 gm. of EDTA was given over a 6-hour period, and a similar fall in serum calcium occurred. On subsequent days, the dose varied from 18 to 22.5 gm. (330 to 440 mg. per kilogram of body weight), as shown in Figure 1, which also shows the serum calcium levels and the urinary calcium excretion. On the 15th hospital day, gross hematuria followed the insertion of a Foley catheter, and on the next day the sputum was blood streaked. By the 20th hospital day the serum calcium had fallen to 7.2 mg. per 100 cc., and administration of the drug was stopped. On the 21st hospital day it was noted that blood drawn for chemical studies did not clot, although no anticoagulant had been added. Later that day the patient passed a large, tarry stool, and severe dyspnea immediately developed. She died 45 minutes later. The serum nonprotein nitrogen rose steadily during the latter part of the course (from 34 mg. per 100 cc., on the 12th hospital day to 93 mg. on the 20th), and the serum phosphorus rose from 3.9 mg. per 100 cc. on the 12th day to 8.9 mg. on the 20th. The serum potassium was 4.4 milliequiv. per liter on admission but fell to vary between 2.7 and 3.9 milliequiv. until the 15th hospital day, when it dropped to 2.0 milliequiv. On the 16th day it was again

*From the Department of Pathology, Massachusetts General Hospital, and the Medical Laboratories of the Collis P. Huntington Memorial Hospital of Harvard University, at the Massachusetts General Hospital.
Publication No. 837 of the Cancer Commission of Harvard University.

†Clinical fellow in pathology, Massachusetts General Hospital, and trainee, National Cancer Institute.

‡Assistant resident in pathology, Massachusetts General Hospital.

§Clinical and research fellow in medicine, Massachusetts General Hospital, and Damon Runyon Research Fellow.

¶Assistant in medicine, Massachusetts General Hospital and Harvard Medical School.

‖Available as Versene from Riker Laboratories, Los Angeles, California.

3.0 milliequiv. and rose to 4.5 milliequiv. on the 20th hospital day. No prothrombin determinations were done.

Autopsy showed extensive carcinomatosis. Tumor studded the pleuras; massive deposits surrounded the inferior vena cava and invaded the mediastinum and retroperitoneum; the liver was extensively replaced, and osteolytic metastases were present in the ribs, clavicles, spine, innominate bones and calvarium. The lungs weighed 400 and 500 gm. Both were mottled, with firm, raised, deep-red areas sharply delimited from the surrounding aerated tissue. The small bowel contained greenish-black fluid, and the large bowel tarry feces. The kidneys weighed 180 gm. each. The cut surfaces bulged

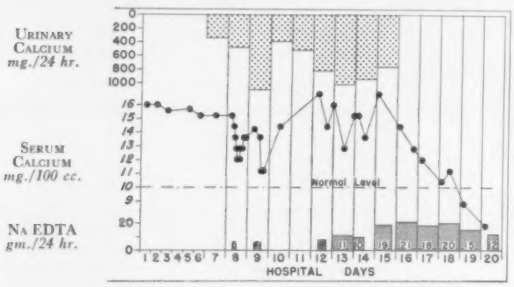


FIGURE 1. *Response to Treatment in Case 1.*

slightly. The spleen weighed 330 gm., and the liver 1800 gm. No blood clots were encountered at any time during the autopsy. All the blood obtainable was filtered through cheesecloth, but no clots were found.

CASE 2. J.G. (M.G.H. 802869),* a 4½-year-old girl, was admitted to the hospital with hypercalcemia after vitamin D therapy for hypoparathyroidism and moniliasis. The serum calcium was 18 mg. per 100 cc. Vitamin D was at once withdrawn, and treatment with sodium EDTA begun. Each day's dose was given intravenously in 1000 cc. of a solution containing dextrose and salts. The daily doses were 2 gm. (130 mg. per kilogram of body weight) or 3 gm. (200 mg. per kilogram), as shown in Figure 2, which also shows the serum calcium levels as estimated by the EDTA and oxalate precipitation methods and the urinary excretion of calcium. The patient did fairly well until the 7th hospital day, when oliguria became evident and grew increasingly severe. Because of the oliguria the drug was withdrawn on the 11th hospital day. A fever that developed on the 7th hospital day subsided with penicillin and oxytetracycline. The serum nonprotein nitrogen, which had been 26 mg. per 100 cc. on the 4th hospital day, rose steadily to 176 mg. on the 17th, and the serum phosphorus rose from 4.8 mg. per 100 cc. on the 6th hospital day to 10.0 mg. on the 16th. She died on the 18th hospital day. The serum potassium level fell slowly from 4.4 milliequiv. per liter on the 11th hospital day to 3.1 milliequiv. on the day before death. The prothrombin activity was 70 per cent of normal on the 4th and 5th, 50 per cent on the 6th, and 60 per cent on the 8th and 9th hospital days.

At autopsy the lungs weighed 145 and 120 gm. In each lobe there were a few firm, dark-red patches that were sharply delineated. The kidneys weighed 67 and 70 gm. The cut surfaces bulged slightly. There were a few petechiae in the proximal jejunum, and the whole jejunoileum was slightly edematous. The liver weighed 500 gm. and was fatty. The spleen weighed 60 gm., the adrenal glands 1.05 and 1.40 gm. The lymph nodes throughout the body were slightly enlarged. Post-mortem clotting was not abnormal.

MICROSCOPICAL FINDINGS

The unexpected findings in the 2 cases were so similar that it will be convenient to consider them together.

*Previously reported in detail.[5]

The general architecture of the organs containing many reticuloendothelial cells was not disturbed. In the spleens the cords and sinusoids were of normal size. The malpighian bodies were small. In the bone marrow in both cases the bony structure was normal, except for areas of destruction by carcinoma in Case 1 and occasional infractions of the ribs in Case 2. The marrow fat was of the usual quantity in the spine, ribs and calvarium in Case 1, and reduced in the spine and ribs in Case 2. Hematopoiesis seemed to be proceeding normally. In the livers there was slight centrilobular fatty change in Case 1, and severe generalized fatty change in Case 2. The lymph nodes were edematous, with widely dilated sinusoids and relatively few lymphocytes. Throughout the reticuloendothelial system the striking abnormality was the presence of large, sharply defined, oval cells measuring up to 30 microns in greatest dimension. The nuclei of these cells was of the vesicular type usually seen in macrophages, and their cytoplasm was filled and apparently distended by coarse, sharply delineated, eosinophilic granules that varied considerably in size. These large cells filled the splenic cords almost to the exclusion of blood cells (Fig. 3*C*). They occasionally lay free in a splenic sinus. They were very numerous in the bone marrow, particularly in Case 2, usually lying in close relation to a sinusoid (Fig. 3*A*). In some lymph nodes

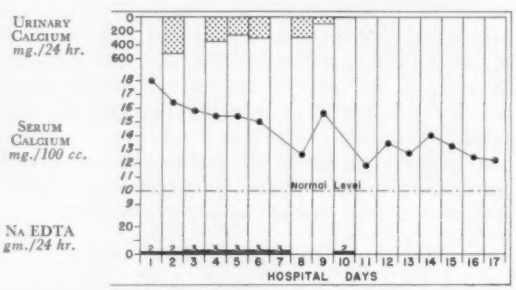


FIGURE 2. *Response to Treatment in Case 2.*

they were very common, lying both within and without the sinusoids. A few such cells were seen in the thymus of Case 2. The morphology of the littoral cells of the spleens, bone marrow, lymph nodes and livers varied. Some were small and without granules, some were large and distended with granules, but the majority were moderately enlarged and contained a small number of granules that tended to be finer than those of the very large cells (Fig. 3*B*). The cells of the germinal centers in the lymph nodes and of the few centers seen in the spleens were filled with granules. The laminae propriae of the jejunoileums and colons contained many of the large, granular cells together with an exudate of lymphocytes and plasma cells (Fig. 4*C*). The staining properties of the granules are shown in Table 1.

The general architecture of the kidneys was within normal limits in both cases. The arteries, arterioles

and glomerular tufts were normal. Near the mouth of a few proximal convoluted tubules there was a piling up of the cells lining Bowman's capsule. Sometimes Bowman's space contained a little eosinophilic precipitate. The most severe damage was in the proximal convoluted tubules, which were moderately dilated but were either empty or contained only a little, pale, eosinophilic precipitate. Their basement membrane was intact, but for the most part they had lost their epithelium (Fig. 4*A*). In some places, epithelial cells persisted but were flat and stretched out, with eosinophilic, granular cytoplasm and nuclei that were often large, atypical and hyperchromatic. No normal epithelium was seen. The loops of Henle were also dilated, though less severely. They contained eosinophilic casts and coarsely granular eosinophilic material. Their epithelium was usually intact, except in the region of the casts, where the cells were often pyknotic. A few of the epithelial cells in the loops contained yellow pigment that did not take the stain for iron. The distal convoluted tubules were dilated, though not so markedly as the proximal. They contained eosinophilic casts and desquamated epithelial cells. The basement membranes were again intact. In places the epithelium had been lost, but not for such large areas as in the proximal tubules. Occasionally, the epithelium was flattened, with large, hyperchromatic nuclei. In other places, groups of epithelial cells were ballooned, each cell being filled almost to the bursting point by a single, large, clear vacuole that pushed the nucleus aside (Fig. 4*B*). The collecting tubules contained eosinophilic and hematoxylinophilic casts, some of which were concentrically laminated. The epithelium was usually intact, though occasionally destroyed in the neighborhood of a cast. Particularly in the rays, an occasional collecting tubule showed the ballooning seen also in the distal convoluted tubules. The interstitium was without inflammatory reaction. In a few places there were small, granular, hematoxylinophilic or eosinophilic masses that lay in relation to a damaged tubule. Some of these masses were polypoid and partially covered by epithelium. The hematoxylinophilic masses did not take von Kossa's stain for calcium. No large, granular cells similar to those of the spleen were seen.

In both cases there was intra-alveolar hemorrhage in the lungs. The hemorrhagic areas were few and small in Case 2 and many and confluent in Case 1, the affected alveoli being filled with blood and edema fluid. There were no inflammatory cells and little fibrin, though in Case 1 some alveoli were lined by a membrane of wavy, fibrillar material that reacted poorly or not at all to the Weigert stain for fibrin. None of the large, granular cells were observed. In Case 1 no lesion was seen to explain the intestinal hemorrhage. In Case 2 the pancreatic ducts contained recent hemorrhage; the blood lay around concretions that were sometimes associated with loss or metaplasia of the epithelium. The concretions did not stain for calcium.

The carcinoma in Case 1 was of cords of poorly differentiated cells. In Case 2 the adrenal cortexes were thin, with a prominent exudate of lymphocytes and plasma cells extending from the capsules. There were solitary foci of monilial growth in the lungs and esophagus. Many blocks from the neck were examined, but though structures that might have been atrophic parathyroid glands were seen, no parathyroid tissue could be identified with certainty.

Discussion

The necrosis of the proximal convoluted tubules of the kidneys was very similar to that reported in cases of poisoning with mercury, uranium and chromates.[9]

Table 1. *Staining Properties of the Cytoplasmic Granules.*

Stain	Color of Granules
Hematoxylin and eosin	Pink
Masson	Light green to brown
van Gieson	Yellow brown
Phloxine and methylene blue	Red
Chromotrope aniline blue	Blue (as collagen)
Giemsa	Red
Periodic acid Schiff	Red
after salivary digestion	Unchanged
Aqueous toluidine blue	Unstained
Aqueous crystal violet	Irregularly blue or reddish purple
Congo red	Unstained
Sudan IV	Unstained
Iron stain	Unstained
Phospholipid (Baker)	Unstained

To this was added a vacuolar change in the epithelium of the distal convoluted and collecting tubules like that reported in cases of chronic diarrhea and hypokalemia.[10-14] Both patients described above had serum potassium levels near the low limit of normal, but, except for a short period in Case 1, the levels never fell far below normal. Both had mild diarrhea. The vacuolization was not similar to "sucrose" or "osmotic" nephrosis, in which the tubular cells are filled by many small vacuoles instead of being distended by a single, large vacuole.[9,15] Both the changes reported in cases of intestinal disease and hypokalemia and those of "sucrose" nephrosis are most common in the proximal convoluted tubules. The absence of vacuolization in the proximal tubules in the cases reported above may have been because the vacuolar changes were hidden by the extensive necrosis.

Chemical studies were done on blood removed from the heart at autopsy in Case 1. The high plasma fibrinogen level, 0.51 gm. per 100 cc. (normal 0.15 to 0.30 gm.), confirmed the assumption that no clotting had taken place. The failure to clot was not due to a lack of calcium, for the blood did not clot on the addition of excess calcium chloride. It did form a stable clot when prothrombin was added. When normal plasma with 100 per cent prothrombin activity was added to an equal quantity of the patient's plasma, the prothrombin activity of the mixture was 50 per cent of normal. The clot did not dissolve on incubation, demonstrating that no fibrinolysin was present. Protamine titration showed no heparin ac-

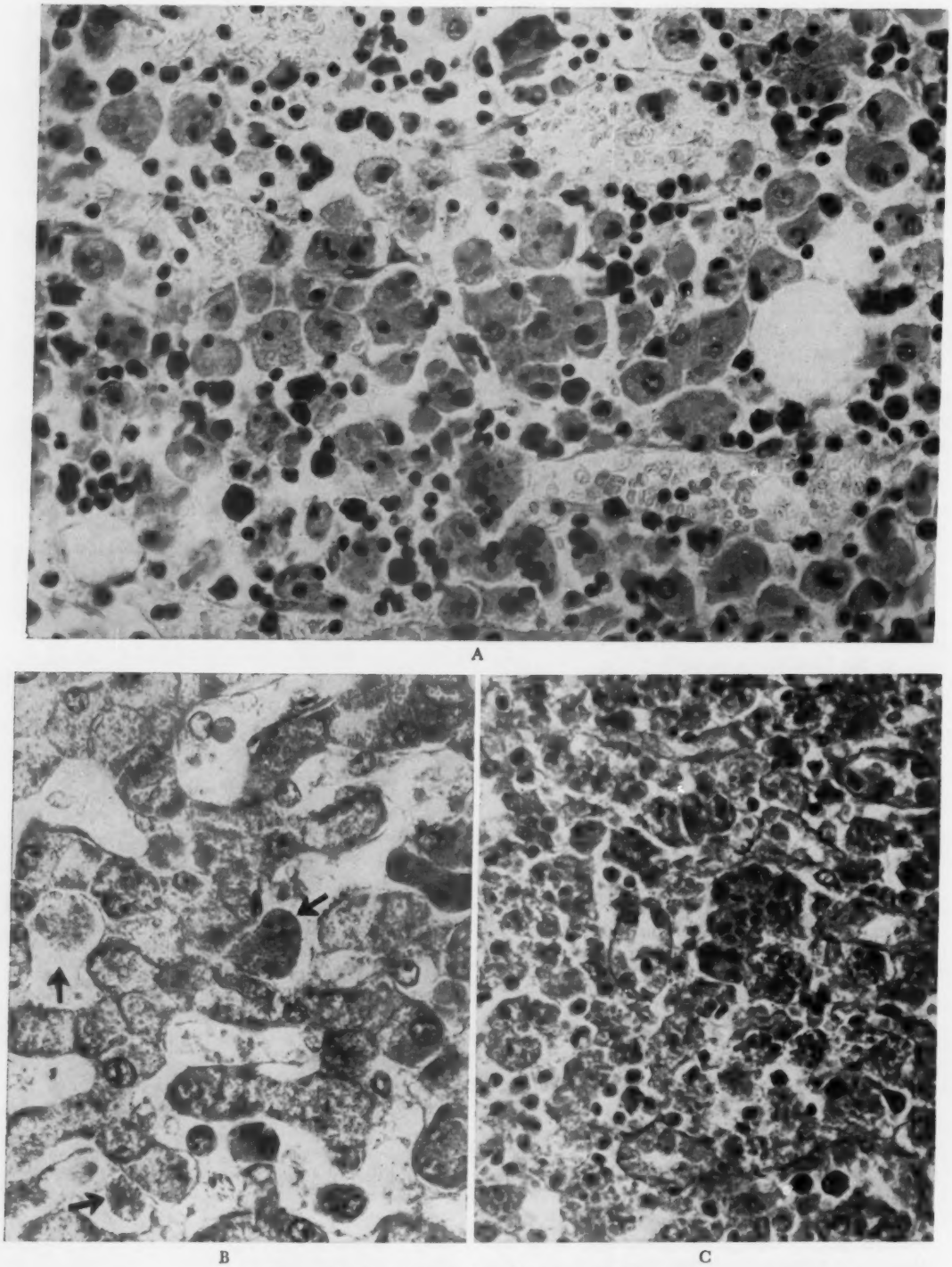


FIGURE 3. *Sections of the Bone Marrow and Spleen.*

A=*bone marrow in Case 2 (phloxine and methylene blue stain x 550).* B=*liver in Case 1 (Masson stain x 550); arrows point to large granular Kupffer cells.* C=*spleen in Case 1 (periodic acid Schiff stain x 550); note the large granular cells that lie between the sinusoids.*

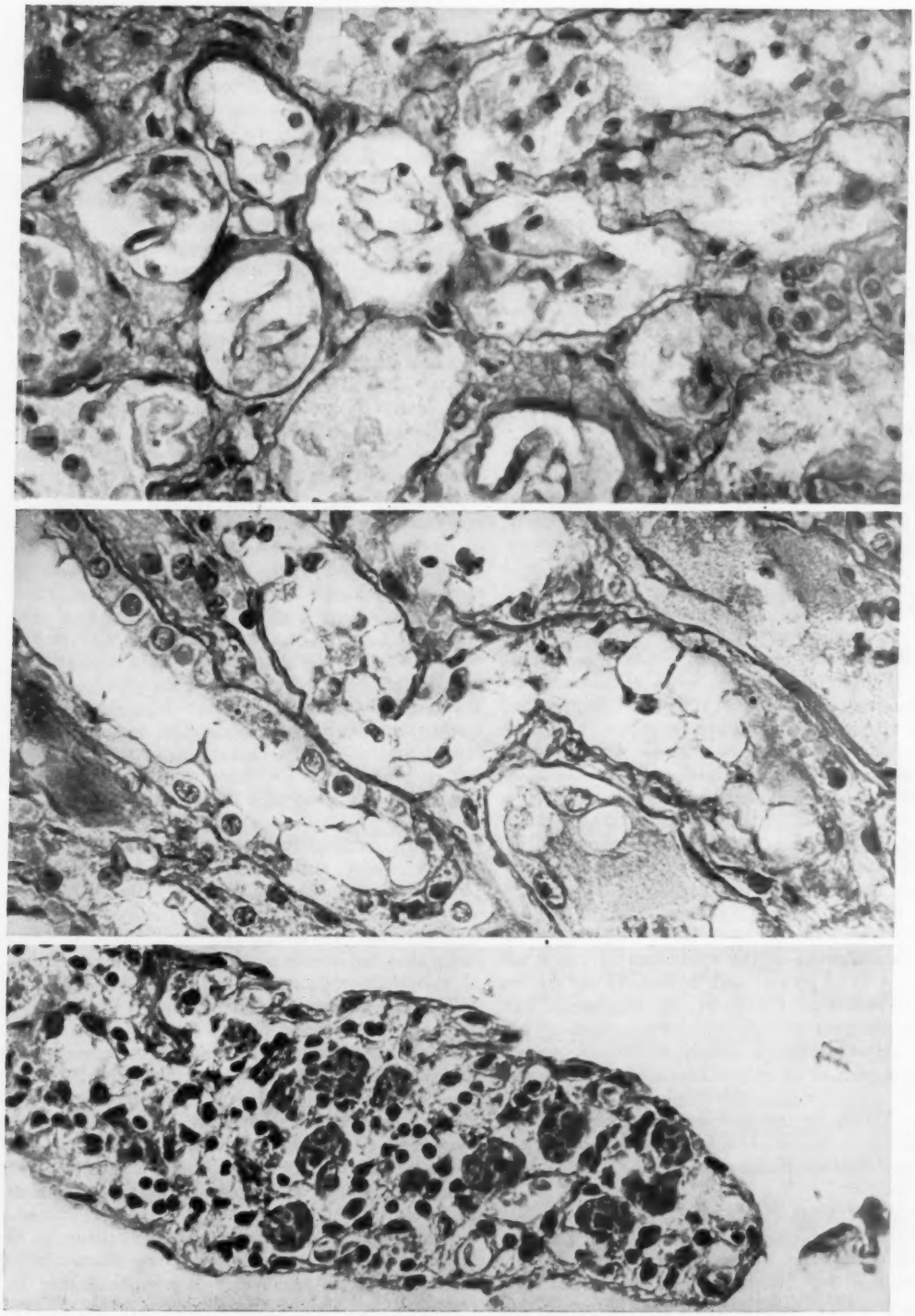


FIGURE 4. *Further Photomicrographs in Cases 1 and 2.*

A=proximal convoluted tubules in Case 2 (periodic acid Schiff stain x 550). B=distal convoluted tubule in Case 1 (Masson stain x 550). Vacuoles distend the tubular epithelial cells. C=jejunoileum in Case 2 (Masson stain x 550). The large granular cells are seen in a villus that has lost the surface epithelium.

tivity. No such studies were done in Case 2, but during the administration of sodium EDTA the plasma prothrombin level fell to 50 per cent of normal. It is not possible to say that the hemorrhages were due solely to a lack of prothrombin, but this lack cannot have been unimportant.

The staining properties of the granules in the large cells of the reticuloendothelial system suggest that they contain either a glycoprotein or a mucoprotein (Table 1). Their distribution and morphology are similar to those of the phagocytes seen after the administration of thorium dioxide, though such phagocytes are smaller and contain less granular material. The appearance of the large, granular cells and their distribution in the jejunoileum and lymph nodes are very like those of the granular cells described in certain cases of Whipple's disease, except that in Whipple's disease the granules are basophilic and stain metachromatically with toluidine blue.[16-19]

The abnormalities were so similar in the 2 cases and formed such an unusual combination that they were probably caused by the same agent or agents. Of the few features common to the cases, the most obvious are hypercalcemia and treatment with sodium EDTA. The morphologic changes in clinical and experimental hypercalcemia have been described in detail.[9,20-22] There may be renal damage, but this consists of calcification of the tubular epithelium and arteriolar changes. No report of either hemorrhagic manifestations or engorgement of the reticuloendothelial system has been found. It is therefore improbable that the lesions were due to hypercalcemia alone.

It remains to consider whether the lesions could have been due to sodium or calcium EDTA, alone or in combination with hypercalcemia. We are aware of only one report of autopsy findings in cases treated with sodium or calcium EDTA.[2] Two women dying with hypercalcemia due to osteolytic metastases were given single doses of 175 mg. and 235 mg. of sodium EDTA per kilogram of body weight intravenously four days before death. Each showed extensive "sucrose" vacuolization of the epithelium of the renal tubules. A third patient with hypercalcemia due to osteolytic metastases was given a single dose of 225 mg. per kilogram of body weight three and a half months before death. No lesions attributable to the drug were seen at autopsy. Clinical reports describing cases treated with repeated doses of sodium or calcium EDTA do not mention either hemorrhagic or renal lesions, though in most cases the daily doses were smaller than those given to the cases under discussion.[2,4,23-27]

In 1 case of acute lead poisoning treated with calcium EDTA, oliguria was prominent, but did not seem due to the drug. Indeed, its administration may have improved renal function.[28] In rats, parenterally administered C^{14}-labeled calcium EDTA rapidly diffuses throughout the body except that it does not enter the red cells and may not enter the brain. It is excreted by the kidneys both by glomerular filtration and tubular secretion, so that 95 to 98 per cent of the dose appears in the urine within six hours, apparently unchanged. Less than 0.1 per cent is metabolized as measured by C^{14} occurring in the expired air.[5] Acute toxicity experiments are scarcely relevant, for if a large dose is given quickly, the animal dies in tetany[3] and repeated experiments utilized animals that were not hypercalcemic. However, since both the patients under discussion were hypercalcemic, it can be assumed that most of the drug was present as the calcium chelate, and so toxicity experiments with calcium EDTA become more important. Rats will tolerate up to 1000 mg. per kilogram of body weight intraperitoneally for as long as fourteen weeks; however, 50 per cent of rabbits given 500 mg. and 50 per cent of cats given 250 mg. per kilogram intraperitoneally daily died in an average time of seventy-eight days. Of dogs given 150 mg. per kilogram intravenously twice a day 50 per cent died in an average time of forty days.[29] Unfortunately, there is no description of the morphologic findings in the animals that died. Studies in vitro suggest that sodium EDTA may interfere with the clotting mechanism other than by reducing the available calcium. At least in some circumstances, it increases the prothrombin time after optimal calcification. The nature of this action is not clear.[30,31]

In sum, there is not adequate evidence that the unusual lesions seen in these cases were due to sodium or calcium EDTA. Nevertheless, it is hard to avoid the conclusion that the drug was in some way concerned with their production. The combination of lesions was uncommon, and they occurred in 2 cases in which the only common feature was hypercalcemia. Hypercalcemia alone does not produce these lesions.

Calcium EDTA may be lethal in animals. It is excreted by the renal tubules as well as the glomeruli. Some sort of damage to the renal tubules has been found in 4 of 5 cases treated with sodium EDTA in which the autopsy findings are known. The drug may interfere with the clotting mechanism. It seems likely that the lesions were due to this agent, either alone or acting with some other factor.

The clinical responses in these cases were similar to those described before.[1,2,4] Administration of the drug caused a prompt fall in serum calcium as estimated by the EDTA and oxalate precipitation methods. That this fall is transient if only a single dose is given can be seen from Figure 1. The studies on postmortem blood in Case 1 confirm that the total circulating calcium is not reduced by administration of the drug.[2] The EDTA and oxalate precipitation methods gave serum calcium values of 10.4 mg. per 100 cc., but pre-ashing showed the total serum calcium to be 26 mg. per 100 cc., the difference being assumed to be calcium bound to EDTA.[32,33] It is probable that the calcium bound is not physiologically active, as suggested by the transient clinical improvement seen in both cases: the serum calcium levels as measured by these methods fell after the start of therapy. How-

ever, it seems that in cases of hypercalcemia the clinical improvement is so slight, and the increase in urinary calcium excretion of so little value, that the use of this therapy should be carefully weighed against the fact that it may cause the serious lesions described here. When it is used, it is essential to keep the urine alkaline if calcium is to be carried from the body in combination with the drug; 1 gm. of EDTA will bind about 100 mg. of calcium at pH 7.4 but only about 50 mg. at pH 6.0, and it releases all its bound calcium, reverting to a sodium salt at pH 5.0.[34,35] Renal damage might result from the release of large quantities of calcium owing to acidification of the urine in transit through the kidney.

Lead and certain other metals have an even greater avidity for EDTA than calcium has. If one of these metals is present it will displace calcium, forming instead a stable, un-ionized metal chelate.[7,35] This property has been utilized in the treatment of acute and chronic lead poisoning and to increase the rate of excretion of certain radioactive metals.[23-25,27,28,36-39] When calcium EDTA is administered parenterally, the metal displaces the calcium, and the resulting metal chelate is excreted by the kidney. Not only is the rate of excretion of the metal thus increased, but also the circulating un-ionized chelate is much less toxic than a similar quantity of ionized metal would be.[25,28,29] It seems unnecessary to give large doses. Small doses have been found adequate clinically, the increase in the rate of excretion of radioactive yttrium produced in rats by a single daily dose being as great as that produced by two such doses daily.[36] Sodium EDTA has also been used to dissolve corneal opacities and urinary calculi.[40-42] It should be remembered that the drug is readily absorbed through the skin.[3,23] Its use as an anticoagulant for blood transfusions seems undesirable.[43]

Summary

Two cases of hypercalcemia treated with sodium EDTA are described. One patient was a woman dying with osteolytic metastases, and the other a child with acute hypercalcemia after vitamin D therapy.

In both cases there was the same combination of three unexpected findings at autopsy: severe damage to the renal tubules, engorgement of the reticuloendothelial cells with coarse, eosinophilic granules, and hemorrhagic manifestations.

Reason is given for thinking that these lesions may have been due to the administration of the drug. The clinical uses of sodium and calcium EDTA are discussed.

References

1. Bellin, J., and Laszlo, D. Metabolism and removal of Ca^{45} in man. *Science* **117**:331-334, 1953.
2. Holland, J. F., Danielson, E., and Sahagian-Edwards, A. Use of ethylene diamine tetra acetic acid in hypercalcemic patients. *Proc. Soc. Exper. Biol. & Med.* **84**:359-364, 1953.
3. Popovici, A., Geschickter, C. F., Reinovsky, A., and Rubin, M. Experimental control of serum calcium levels in vivo. *Proc. Soc. Exper. Biol. & Med.* **74**:415-417, 1950.
4. Spencer, H., Vankinscott, V., Lewin, I., and Laszlo, D. Removal of calcium in man by ethylenediamine tetra-acetic acid: metabolic study. *J. Clin. Investigation* **31**:1023-1027, 1952.
5. Foreman, H., Vier, M., and Magee, M. Metabolism of C^{14}-labelled ethylenediaminetetraacetic acid in rat. *J. Biol. Chem.* **203**: 1045-1053, 1953.
6. Hart, H., and Laszlo, D. Modification of distribution and excretion of radioisotopes by chelating agents. *Science* **118**:24, 1953.
7. Schwarzenbach, G., and Ackermann, H. Komplexion. XII. Die Homologen der Aethylendiamintetraessigsaure und ihre Erdalkalikomplexe. *Helvet. chim. acta* **31**:1029-1048, 1948.
8. Case Records of the Massachusetts General Hospital (Case 40361). *New Eng. J. Med.* **251**:442-448, 1954.
9. Allen, A. C. *The Kidney: Medical and surgical diseases.* 583 pp. New York: Grune & Stratton, 1951.
10. Jensen, E. S., Baggenstoss, A. H., and Bargen, J. A. Renal lesions associated with ulcerative colitis. *Am. J. M. Sc.* **219**:281-290, 1950.
11. Keye, J. D., Jr. Death in potassium deficiency: report of case including morphologic findings. *Circulation* **5**:766-770, 1952.
12. Kulka, J. P., Pearson, C. M., and Robbins, S. L. Distinctive vacuolar nephropathy associated with intestinal disease. *Am. J. Path.* **26**:349-377, 1950.
13. Odessky, L., and Burdison, W. R. Intestinal lipodystrophy (Whipple's disease) occurring with parathyroid hyperplasia and nephrosis: report of case with autopsy. *Arch. Path.* **49**:307-320, 1950.
14. Perkins, J. G., Petersen, A. B., and Riley, J. A. Renal and cardiac lesions in potassium deficiency due to chronic diarrhea. *Am. J. Med.* **8**:115-123, 1950.
15. Anderson, W. A. D. Sucrose nephrosis and other types of renal tubular injuries. *South. M. J.* **34**:257-263, 1941.
16. Jones, C. M., Benson, J. A., Jr., and Roque, A. L. Whipple's disease: report of case with special reference to histochemical studies of biopsy material and therapeutic results of corticosteroid therapy. *New Eng. J. Med.* **248**:665-670, 1953.
17. Plummer, K., Russi, S., Harris, W. H., Jr., and Caravati, C. M. Lipophagic intestinal granulomatosis (Whipple's disease): clinical and pathologic study of 34 cases, with special reference to clinical diagnosis and pathogenesis. *Arch. Int. Med.* **86**:280-310, 1950.
18. Rosen, M. S., and Rosen, S. H. Intestinal lipodystrophy of Whipple: report of case and analysis of literature. *Am. J. Path.* **23**:443-461, 1947.
19. Upton, A. C. Histochemical investigation of mesenchymal lesions in Whipple's disease. *Am. J. Clin. Path.* **22**:755-764, 1952.
20. Anderson, W. A. D. Hyperparathyroidism and renal disease. *Arch. Path.* **27**:753-778, 1939.
21. Goormaghtigh, N., and Handovsky, H. Effect of vitamin D_2 (calciferol) on dog. *Arch. Path.* **26**:1144-1182, 1938.
22. Mulligan, R. M. Metastatic calcification associated with hypervitaminosis D and haliphagia. *Am. J. Path.* **22**:1293-1305, 1946.
23. Foreman, H., Hardy, H. L., Shipman, T. L., and Belknap, E. L. Use of calcium ethylenediaminetetraacetate in cases of lead intoxication. *Arch. Indust. Hyg.* **7**:148-151, 1953.
24. Conference on use of calcium ethylenediaminetetraacetate in treating heavy-metal poisoning. *Arch. Indust. Hyg.* **7**:137-147, 1953.
25. Hardy, H. L., Elkins, H. B., Ruotolo, B. P. W., Quinby, J., and Baker, W. H. Use of monocalcium disodium ethylene diamine tetra-acetate in lead poisoning. *J.A.M.A.* **154**:1171-1175, 1954.
26. Rubin, M., Gignac, S., Bessman, S. P., and Belknap, E. L. Enhancement of lead excretion in humans by disodium calcium ethylenediamine tetraacetate. *Science* **117**:659, 1953.
27. Sidbury, J. B., Jr., Bynum, J. C., and Fetz, L. L. Effect of chelating agent on urinary lead excretion: comparison of oral and intravenous administration. *Proc. Soc. Exper. Biol. & Med.* **82**: 226-228, 1953.
28. Bessman, S. P., Ried, H., and Rubin, M. Treatment of lead encephalopathy with calcium disodium Versenate: report of case. *M. Ann. District of Columbia* **21**:312-315, 1952.
29. Bauer, R. O., Rullo, F. R., Spooner, C., and Woodman, E. Acute and subacute toxicity of ethylene diamine tetraacetic acid (EDTA) salts. *Federation Proc.* **11**:321, 1952.
30. Zucker, M. B. Some effects of disodium ethylenediamine tetraacetate on blood coagulation. *Am. J. Clin. Path.* **24**:39-41, 1954.
31. Cronkite, E. P., and Jacobs, G. J. Species differences in influence of Sequestrone (EDTA) on prothrombin assay methods. *Clin. Res. Proc.* **2**:62, 1954.
32. Elliott, W. E. Volumetric determination of calcium in blood serum. *J. Biol. Chem.* **197**:641-644, 1952.
33. Fiske, C. H., and Logan, M. A. Determination of calcium by alkalimetric titration. II. Precipitation of calcium in presence of magnesium, phosphate and sulfate, with applications to analysis of urine. *J. Biol. Chem.* **93**:211-266, 1931.
34. *The Versenes.* (Technical Bulletin No. 2.) Seventh edition. Framingham, Massachusetts: Bersworth Chemical Company, 1954.
35. Martell, A. E., and Calvin, M. *Chemistry of the Metal Chelate Compounds.* 613 pp. New York: Prentice-Hall, 1952.
36. Cohn, S. H., Gong, J. K., and Fishler, M. C. Studies on EDTA treatment of internal radioactive contamination. *Nucleonics* **11**: 56-61, 1953.
37. Hamilton, J. G., and Scott, K. G. Effect of calcium salt of Versene upon metabolism of plutonium in rat. *Proc. Soc. Exper. Biol. & Med.* **83**:301-305, 1953.
38. Mitchell, W. G. Antagonism of toxicity of vanadium by ethylenediamine tetra acetic acid in mice. *Proc. Soc. Exper. Biol. & Med.* **83**:346-348, 1953.
39. Foreman, H., Fuqua, P. A., and Norwood, W. D. Experimental administration of ethylenediamine-tetraacetic acid in plutonium poisoning. *Arch. Indust. Hyg.* **10**:226-231, 1954.
40. Gehres, R. F., and Raymond, S. New chemical approach to dissolution of urinary calculi. *J. Urol.* **65**:474-483, 1951.
41. Grant, W. M. New treatment for calcific corneal opacities. *Arch. Ophth.* **48**:681-685, 1952.
42. Raymond, S. and Gehres, R. F. Ethylenedinitrilotetraacetic acid as solvent for urinary calculi. *Proc. Soc. Exper. Biol. & Med.* **74**: 715, 1950.
43. Proescher, F. Anticoagulant properties of ethylene bis-iminodiacetic acid. *Proc. Soc. Exper. Biol. & Med.* **76**:619, 1951.

SUCCESSFUL CALCIUM DISODIUM ETHYLENE DIAMINE TETRA-ACETATE TREATMENT OF LEAD POISONING IN AN INFANT*

LEIGHTON A. KNELLER, M.D.,† HENRY S. M. UHL, M.D.,‡ AND JACOB BREM, M.D.§

WORCESTER, MASSACHUSETTS

LEAD poisoning is a common and serious problem. Intoxication in children frequently results from household contacts and ingestion of the nonvolatile inorganic forms of lead, and in adults from inhalation of industrial volatile organic forms. Total infant mortality from plumbism is as high as 30 per cent, increasing to 65 per cent with the complication of encephalopathy.[1]

Rational therapy for plumbism followed the study of lead metabolism by Aub and his co-workers[2] (1925), who recommended a high-calcium intake to aid in the deposition of lead into the bones. Kety and Letonoff[3] gave sodium citrate intravenously, and this treatment has been the method of choice, especially for lead colic.[4] BAL therapy, employed with varying results for lead intoxication,[1,4] has proved less satisfactory in clinical use than observers had anticipated from in vitro studies.

Recently, lead intoxication has been treated with the organic complexing agent, ethylene diamine tetra-acetic acid (EDTA),¶ and reports from several investigators[4,5-9] have been encouraging. A further case is reported because of the excellent result obtained, the modified technic of administration and the complication encountered. The method appears to be safe, practical, effective and readily usable in any community hospital.

METHODS

Administration

A solution consisting of 0.5 gm. of calcium disodium EDTA in 100 cc. of physiologic saline solution was given by subcutaneous clysis. Both thighs and the subscapular areas of the back were chosen as sites of injection. At first hyaluronidase was used, but rotation of the sites of injection obviated the necessity for the enzyme. The clyses, administered three times daily for five days, were given over a one-hour period, and the absorption occurred between one and a half and two hours. There was neither local tissue damage nor reaction, and the patient tolerated the procedure well.

Collection of Specimens

The methods of collecting and preserving blood and urine samples have great practical importance. Since rubber tubing, ordinary glassware and cork contain significant quantities of lead, all glassware used was Pyrex, and all tubing plastic; the corks were coated with wax. The blood samples were centrifuged, and the plasma and cells separated. The lead content of the blood and urine samples (Table 1) was determined by Dr. S. P. Bessman at the Research Foundation of Children's Hospital, Washington, D. C.

CASE REPORT

J. B., a 20-month-old male infant,‖ was admitted to the hospital on October 6, 1953, because of persistent vomiting. During the previous 5 weeks although his appetite remained excellent, he had intermittent periods of vomiting, sometimes projectile and generally occurring soon after eating. After a transient remission about 3 weeks before admission, he lost 4.5 kg. in weight and became pale, irritable, lethargic, disinterested and constipated. He kept his knees flexed and cried if his abdomen was pressed. He had fallen down 2 stairs, without apparent ill effect. The mother stated that her house was relatively old, without recent painting, and that the patient was in the habit of chewing on the windowsills.

The past and family histories were noncontributory.

Physical examination revealed a well developed, emaciated, pale, lethargic, fretful, acutely ill child with a strong cry who weighed 9 kg. The cranial sutures were closed. The pupils were round, regular and equal, and reacted well to light. There were no ocular palsies, and the fundi appeared normal. There was no "lead line" on the gums. The heart and lungs were normal. There was generalized abdominal tenderness, with mild spasm, but no evidence of hepatomegaly, muscle rigidity, tremors or convulsions and no abnormal reflexes.

The temperature was 98.2°F. (by rectum), the pulse 92 and the respirations 24. The blood pressure was 100/60.

Examination of the blood showed a red-cell count of 3,810,000, with a hemoglobin of 11.5 gm. per 100 cc. (75 per cent), and a white-cell count of 26,000, with 66 per cent neutrophils, 28 per cent lymphocytes, 4 per cent monocytes, 1 per cent basophils and 1 per cent eosinophils. There was slight basophilic stippling to the red cells. Urinalysis revealed a clear, alkaline urine with a trace of albumin, a green reaction to Benedict's solution and a ++++ test for acetone, with 10 to 20 white blood cells per high-power field in the sediment. The blood nonprotein nitrogen was 25 mg., and the blood sugar 66 mg. per 100 cc. The carbon dioxide combining power was 67.2 vol. per cent. Lumbar puncture disclosed crystal-clear spinal fluid under a pressure equivalent to 360 mm. of water, with a sugar of 90 mg. and a total protein of 50 mg. per 100 cc. and 2 lymphocytes per high-power field. Roentgenograms of the ribs showed typical zones of increased density at the costochondral junctions, and films of the long bones demonstrated increased densities at the metaphyses. An electroencephalogram taken while the patient was sleeping was normal.

Immediate treatment consisted of the correction of dehydration and acidosis with parenteral administration of fluids. On the 2d day, a mucopurulent nasal discharge developed, and penicillin, 200,000 units twice daily by mouth, was begun, with rapid improvement. The patient was treated symptomatically for 8 days and given frequent small feedings of a regular diet supplemented with multivitamins. Irritability, constipation, pallor and pica persisted, but vomiting ceased. On the 9th hospital day, therapy with the

*From the Division of Pediatrics and the Department of Medical Education, Worcester City Hospital.

†Formerly, intern, Worcester City Hospital.

‡Director of Medical Education and chief, Department of Education, Worcester City Hospital.

§Assistant pediatrician, Worcester City Hospital; pediatrician, St. Vincent Hospital; formerly, assistant in pediatrics, Tufts College Medical School.

¶Kindly supplied as Versene by the Bersworth Chemical Company, Framingham, Massachusetts.

‖Referred by Dr. H. H. Poras of Clinton, Massachusetts.

calcium-disodium salt of EDTA was instituted, 0.5 gm. in 100 cc. of physiologic saline solution being given by clysis 3 times a day for 5 days. On the 2d day of therapy oliguria, which was partially due to poor fluid intake, developed. On the next day the carbon dioxide combining power was 66 vol. per cent, and the blood nonprotein nitrogen 26 mg. per 100 cc.; the white-cell count was 9700, with a normal differential, and the red-cell count 3,900,000. The urine contained a trace of albumin. On the 5th day of therapy the patient, who looked and acted better, was eating well, retaining food and showing interest in his surroundings. Repeat roentgenograms of the long bones showed no change.

On the 18th hospital day a 2d course of EDTA therapy was given, the same technic and dosage being used; during the subsequent 24 hours, the patient received 3 clyses (total of 1.5 gm.). Symptoms of increased irritability, lethargy and pale, dry skin, sunken eyes and ataxia were then noticed, in addition to continuous coarse tremors of the extremities and jaw, chattering of the teeth and vomiting. Chvostek and Trousseau signs were negative, and no carpopedal spasms were noted. The red-cell count was 4,100,000, the hemoglobin 9.0 gm. per 100 cc. (58 per cent), and the blood calcium 16 mg. per 100 cc. Urinalysis revealed an alkaline urine with a + test for sugar and a trace of acetone. Therapy was discontinued and supportive treatment begun. Intravenous infusions of fluids, consisting of 5 per cent glucose and water, 5 per cent glucose and saline solution and 1/6 molar lactate, were given. He also received 2 whole-blood transfusions totaling 225 cc. During the next 72 hours, he improved greatly, and the tremors ceased. The red-cell count was 4,100,000, and the hemoglobin 81 per cent (Sahli). The blood calcium level fell to 11.0 mg. per 100 cc. The urine was clear and free from sugar or acetone.

The general improvement continued, and the patient was discharged on the 33d hospital day, when he seemed in good health and weighed 10 kg. When he was seen 2 months later he had gained 2 kg., had good color and was very cheerful, affable and active. The hemoglobin was 90 per cent (Sahli). He had had no recurrence of symptoms.

Discussion

In the diagnosis of lead intoxication on the basis of clinical and laboratory findings, children generally present a history of pica, weight loss or failure to gain weight, constipation, lethargy, mental retardation, convulsions and pallor out of proportion to the anemia present; when encephalopathy occurs there may be separation of the suture lines of the skull, papilledema, hypertension, bradycardia and muscular inco-ordination. Adults present colicky abdominal pain, peripheral neuritis and "lead line" of the gums as the main complaints. With the exception of the determination of lead levels in the blood and urine there are no specific diagnostic laboratory tests; however, Byers, Maloof and Cushman[10] have shown that lead intoxication may be associated with a normal twenty-four-hour output of lead in the urine. In such cases elevated levels of urine coproporphyrin excretion[10] would be helpful in confirming the clinical impression.

Routine laboratory procedures may indicate plumbism. The anemia is normocytic and hypochromic; basophilic stippling is a nonspecific finding. Except for mild degrees of hypoproteinemia, albuminuria and glycosuria, studies of the blood and urine are within normal limits. X-ray examination of the abdomen shows radiopaque flakes of ingested material, and that of the chest reveals sharply demarcated, dense zones of thickened spongiosa at the anterior costochondal junctions, forming a chainlike pattern on each side of the sternum.[11] Since the "lines" are due to thickened spongiosa and not the lead per se, simple removal of the element will not alter the x-ray appearance for some time. Similar "lines" may be seen in poisoning with phosphorus, bismuth and titanium and in increased vitamin D intake and healing rickets.[11] Lumbar puncture in patients with encephalopathy reveals a clear spinal fluid under increased pressure, with an elevated protein and occasional white cells. With the proper collection of samples, values for lead above 70 microgm. per 100 cc. of whole blood and from 55 to 80 microgm. per liter of urine are abnormal; the excretion of more than 80 microgm. per liter of urine in twenty-four hours is considered diagnostic.[10] In the case reported above, initial blood and urine levels were correspondingly high, 106 microgm. per 100 cc. and 183 microgm. per liter, respectively (Table 1).

Table 1. *Specific Therapy and Lead Concentration in the Blood and Urine.*

Hospital Day	Day of Therapy	Calcium EDTA		Lead Concentration	
		Amount	Time of administration	Blood	Urine*
		gm.		*microgm./100 cc.*	*microgm./liter*
9	1	0.25	0900 a.m.	106	183
		0.5	0500 p.m.	145	18,100
		0.5	0800 a.m.	76	35,500
10	2	1.5		48	26,500
11	3	1.5			
12	4	1.5			
13	5	1.5		122	—

*Last urine specimen, taken on 13th hospital day, lost in transit to Washington, D. C.

Methods of administration of EDTA and its sodium and calcium salts by all routes have been studied extensively in animals and have shown that the drug is effective when given either parenterally or orally in experimental lead poisoning.[6,12] In human patients the intraperitoneal method is impractical; oral administration, because of variable rates of absorption and the formation of lead chelates in the upper gastrointestinal tract, is uncertain, and the intramuscular route painful and unsuitable for large doses. Therefore, the intravenous or subcutaneous route offers the best method of administration in man. In adults repeated venipunctures and slow infusions have presented little difficulty, but in children the general restlessness and the small caliber of the veins make these procedures difficult and traumatic. At the suggestion of Bessman[13] subcutaneous clyses were employed in the case reported above, and this method proved most advantageous.

The pharmacology of EDTA has been studied in great detail in animals.[12] Acute toxicity of the

sodium salt is due to hypocalcemia, and this effect can be avoided by administration of the solution over a prolonged period. One of us has administered daily for three weeks as much as 5 gm. to adults, with no acute or chronic toxicity; these courses were repeated several times over a period of months. However, a recent report describes the development of acute nephrosis in a child with hypercalcemia treated for eleven days with sodium EDTA in doses of 2 to 3 gm. daily.[14] Studies using the preformed calcium-disodium chelate, on the other hand, have shown no toxicity by all routes.[5-8,12] Bessman et al.[7] report the intravenous administration of 750 mg. daily for twelve days to a three-year-old child, with no toxic signs.

The patient described above was treated with calcium disodium EDTA by clysis for the reasons stated. The clinical response was dramatic, and correlated well with the marked increase in the urinary excretion and the fall in the blood level of lead (Table 1).* Recently, Bessman, Rubin and Leikin[15] reported the successful therapy of 6 out of 7 children with lead encephalopathy with no toxicity from the drug; the child who died probably was treated insufficiently, having received only 0.5 gm. of EDTA. Byers and Maloof,[16] describing the use of calcium EDTA in 5 children with chronic lead poisoning, 3 of whom had encephalopathy, state enthusiastically that "clinical evidence of plumbism rapidly clears." They emphasize, however, the fact that much lead remains stored in the skeleton and that metabolic stresses, such as fever, acidosis, or alkalosis may stimulate the release of this lead from the bones, with recurrence of lead poisoning. Prompt retreatment with EDTA is recommended if such an episode occurs within a year of the initial diagnosis.

The occurrence of hypercalcemia in our patient at the time of EDTA therapy, in association with signs and symptoms of central-nervous-system dysfunction, was unexpected and has not been described by other authors. The clinical findings were neither characteristic of hypocalcemia nor explicable by hypercalcemia. It is possible that the high serum calcium level was due in part to a rapid exchange for readily available lead cations, thus freeing calcium ions into the plasma. We have no explanation for the occurrence of this episode but believe, in view of the ultimate excellent result from therapy, that it was of no serious pathologic consequence.

We are in agreement with the several recent reports on the successful use of EDTA in lead intoxication. The parenteral solution, which is simple to prepare, convenient to administer and free of toxic effects, provides rapid and complete alleviation of symptoms, and, as shown by Bessman et al.,[15] this therapy may well be life saving in severe cases with encephalopathy.

*Separate values for red blood cells and plasma will be presented elsewhere by Dr. Bessman at a later date.

Summary and Conclusions

Lead intoxication is a prevalent and important disease with a high morbidity, especially in children.

A case of lead intoxication and encephalopathy in a twenty-month-old child is presented, together with clinical and laboratory findings necessary to establish a diagnosis.

A brief outline of the historical treatment of lead poisoning and a commentary on the diagnostic procedures are given. The use of a new therapeutic agent, EDTA (ethylene diamine tetra-acetic acid), or "Versene," is discussed. A modified method of administration of the calcium disodium salt useful in pediatrics and general medicine is described.

Calcium EDTA is effective and easily administered. It is recommended as the drug of choice in lead intoxication.

The patient was seen approximately a year after discharge from the hospital. His general health was excellent; the height was 90 cm., and the weight 13.8 kg. Physical development was normal, but there was definite retardation in speech. Neurologic examination was negative. A repeat electroencephalogram was reported as normal. Repeat roentgenograms of the lower extremities showed some "growth" lines where the previous "lead" lines had been noted.

References

1. Ennis, J. M., and Harrison, H. E. Treatment of lead encephalopathy with BAL (2.3-dimercaptopropanol). *Pediatrics* **5**:853-867, 1950.
2. Aub, J. C., Faihall, L. T., Minot, A. S., and Reynikoff, P. Lead poisoning. *Medicine* **4**:1-250, 1925.
3. Kety, S. S., and Letonoff, T. V. Treatment of lead poisoning by sodium citrate. *Am. J. M. Sc.* **205**:406-414, 1943.
4. Agerty, H. A. Symposium on pediatrics: lead poisoning in children. *M. Clin. North America* **36**:1587-1597, 1952.
5. Foreman, H., Hardy, H. L., Shipman, T. L., and Belknap, E. L. Use of calcium ethylenediamine tetraacetate in cases of lead intoxication. *Arch. Indust. Hyg.* **7**:148-151, 1953.
6. Foreman, H., et al. Use of calcium ethylenediaminetetraacetate in treating heavy-metal poisoning. *Arch. Indust. Hyg.* **7**:137-147, 1953.
7. Bessman, S. P., Ried, H., and Rubin, M. Treatment of lead encephalopathy with calcium disodium Versenate: report of case. *M. Ann. District of Columbia* **21**:312-315, 1952.
8. Rubin, M., Gignac, S., Bessman, S. P., and Belknap, E. L. Enhancement of lead excretion in humans by disodium calcium ethylenediamine tetraacetate. *Science* **117**:659, 1953.
9. Sidbury, J. B. Jr., Bynum, J. C., and Fetz, L. L. Effect of chelating agent on urinary lead excretion: comparison of oral and intravenous administration. *Proc. Soc. Exper. Biol. & Med.* **82**: 226-228, 1953.
10. Byers, R. K., Maloof, C. A., and Cushman, M. Urinary excretion of lead in children. *Am. J. Dis. Child.* **87**:548-558, 1954.
11. Keefer, G. P., and Mokrohisky, J. F. Lead poisoning: roentgenograms of chest as aid in diagnosis. *J. Pediat.* **43**:146-151, 1953.
12. *Pharmacology, Physiology, Biochemistry and Toxicity of Versenes.* Framingham, Massachusetts: Bersworth Chemical Company, 1952.
13. Bessman, S. P. Personal communication.
14. Case Records of the Massachusetts General Hospital (Case 40361). *New Eng. J. Med.* **251**:442-448, 1954.
15. Bessman, S. P., Rubin, M., and Leikin, S. Treatment of lead encephalopathy: method for removal of lead during acute stage. *Pediatrics* **14**:201-208, 1954.
16. Byers, R. K., and Maloof, C. A. Edathamil calcium-disodium (Versenate) in treatment of lead poisoning in children. *Am. J. Dis. Child.* **87**:559-569, 1954.

URETEROILEOSTOMY, AN EFFICACIOUS METHOD OF URINARY DIVERSION*

Report of Six Cases

GEORGE R. READ, M.D.,† AND ALFRED HURWITZ, M.D.‡

WEST HAVEN, CONNECTICUT

THE multiplicity of surgical procedures proposed[1] to divert the urinary stream after total cystectomy shows that there has been no satisfactory solution to the major problems of obstruction, infection and hyperchloremic acidosis.

Nephrostomy and cutaneous ureterostomy are not usually efficacious because they require intubation, which almost always leads to progressive pyelonephritis.

In 1911 Coffey[2] advocated tunneling of the ureter through the sigmoid wall to prevent reflux of bowel contents. Stricture of the anastomosis tended to occur, leading to obstruction and ascending infection. A long-term follow-up study on 144 ureterosigmoidostomies of this type for exstrophy of the bladder[3] at the Mayo Clinic showed a 70 per cent occurrence of pyelonephritis. Only 34 per cent of 41 patients studied had normal pyelograms. Half the patients were dead within twenty years of operation.

The mucosa-to-mucosa technic of ureterointestinal anastomosis, described independently in 1949 and 1950 by Nesbit[4] and Cordonnier,[5] has decreased the rate of obstruction to 55 per cent in a series of 54 cases followed for periods ranging from ten months to two and a half years.[6] Pyelonephritis, reported in 44 per cent of these cases, however, indicated that reflux[6-8] was also a frequent complication of this procedure.

In 1951 Leadbetter[9] described a technic combining the use of a tunnel with a mucosa-to-mucosa anastomosis. Another procedure based on the same principles has recently been proposed by Mathisen.[10] A recent, but as yet unpublished, report by Leadbetter[11] indicates that his "combined" technic has significantly lowered the frequency of obstruction and infection.

Hyperchloremic acidosis, which frequently follows ureterosigmoidostomy,[12] is dependent on chloride absorption from the bowel.[13,14] Its occurrence is favored by prolonged exposure of urine to a large absorbing surface.[15] Brunschwig and Lüscher[16] have observed that this disturbance occurs even with "wet" colostomies. Experimental and clinical observations by Lapides[13] indicate that hyperchloremic acidosis, occasionally accompanied by hypokalemia,[17,18] most frequently appears in patients with renal damage.

In an attempt to eliminate infection, several methods of ureterointestinal diversion based on the principle of excluding the site of anastomosis from the fecal stream have been proposed.[19-23] These procedures consist of diverting the ureters into an isolated segment of the gastrointestinal tract. Attempts to construct continent artificial urinary reservoirs capable of completely evacuating their contents have so far been unsuccessful.[23,24] In principle, bowel loops large enough to be utilized as reservoirs are undesirable, for they encourage electrolyte absorption.

In 1950 Bricker[22] described a method of ureterointestinal diversion in which the ureters were transplanted into a short isolated segment of terminal ileum, the distal end of which was exteriorized as an ileostomy. In addition to reducing the likelihood of infection, it was hoped that a short segment of small bowel utilized as a conduit and not as a reservoir would prevent hyperchloremic acidosis.[15]

In 1952 Bricker[26] reported 55 cases of ureteroileostomy, 28 of which were analyzed in detail, with follow-up periods ranging from six to twenty-two months. The operative mortality for the procedure was 3.2 per cent. Pyelograms were reviewed in terms of individual "renal units." Postoperative renal units that were normal or showed only minimal hydronephrosis were considered "satisfactory."

Of the 35 renal units that were normal preoperatively, 20 (71 per cent) were "satisfactory" after surgery, although only 18 (51 per cent) were pyelographically normal. This compares favorably with Cordonnier's[5,6] report of 45 per cent normal pyelograms after ureterosigmoidostomy by a similar mucosa-to-mucosa technic.

The effects of ileal diversion on renal units that were hydronephrotic before operation were particularly encouraging.[26] All degrees of obstruction improved. Eight of 20 units (40 per cent) resumed normal function postoperatively. Four of 7 units that were nonfunctioning preoperatively gave definite pyelographic evidence of function after ureteroileostomy. Figures as encouraging as these have not been reported by other methods of diversion.

Bricker's[26] rate of pyelonephritis was 28 per cent. This is a definite improvement over the 44 per cent reported by Cordonnier[6] and the 70 per cent reported from the Mayo Clinic with the Coffey technic.[3]

Hyperchloremic acidosis was not observed in Bricker's[26] series, in spite of the fact that postoperatively 29 of 55 renal units showed varying degrees of

*Presented at the thirty-fifth annual meeting of the New England Surgical Society, Bretton Woods, New Hampshire, October 8 and 9, 1954.
From the departments of Urology and Surgery, Veterans Administration Hospital, and Yale University School of Medicine.
Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements made and the conclusions drawn by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

†Clinical instructor in urology, Yale University School of Medicine; chief, Urology Section, Veterans Administration Hospital.

‡Associate clinical professor of surgery, Yale University School of Medicine; chief, Surgical Service, Veterans Administration Hospital.

dilatation by pyelogram. With similar degrees of hydronephrosis after ureterosigmoidostomy, biochemical and clinical evidence of hyperchloremic acidosis would have been observed.[12,13]

Case Reports

During the past two years we have performed the Bricker type of ureteroileostomy on 6 patients. Although this series is too small for statistical interpretation, favorable impressions of this method of diversion have been obtained. There were no operative deaths. Follow-up periods range from three to twelve months.

Case 1. A 56-year-old man was admitted to the Newington Veterans Administration Hospital on November 23, 1952, complaining of hematuria of 5 days' duration. Eleven months previously a segmental resection in the region of the left ureteral orifice had been performed for papillary transitional-cell carcinoma.

Physical examination was noncontributory. Laboratory examinations were within normal limits, including a nonprotein nitrogen of 34 mg. per 100 cc. and a carbon dioxide of 21 milliequiv. and chloride of 105 milliequiv. per liter. Intravenous pyelograms were normal.

On November 25 the bladder wall was inadvertently perforated while a transurethral biopsy of a recurrent tumor at the site of previous segmental resection was being performed. A repeat intravenous pyelogram on December 15 revealed a Grade 1 hydronephrosis on the left. Two days later total cystectomy, with prostatoseminal vesiculectomy and ileal diversion, was performed. The immediate postoperative course was complicated by a wound evisceration on the 7th postoperative day. It was necessary to ligate the superficial femoral veins on February 13, 1953, because of thrombophlebitis and suspected pulmonary embolus. On April 24 an abdominal-wall nodule was biopsied and found to contain metastatic tumor from the bladder. From that time on the patient progressively failed, and he died on August 14. Postmortem examination revealed extensive carcinomatosis.

During the entire postoperative course, the nonprotein nitrogen, carbon dioxide and chloride levels were within normal limits. Grade 1 hydronephrosis on the left, still present in the early postoperative period, returned to normal a month after diversion. Periodic intravenous pyelograms were normal thereafter. Pyelonephritis was not observed.

Case 2. A 55-year-old man was admitted to the Newington Veterans Administration Hospital on June 10, 1953, complaining of intermittent hematuria of 3 months' duration. Physical examination was negative. Laboratory data were within normal limits, including a nonprotein nitrogen of 33 mg. per 100 cc. and a carbon dioxide of 27 milliequiv. and chloride of 96 milliequiv. per liter. Intravenous pyelograms were normal on the left but showed a nonfunctioning kidney on the right.

Transurethral biopsy on the day of admission revealed a large papillary carcinoma, with superficial muscle invasion involving the trigone and the right ureteral orifice. On June 17 a total cystectomy, with prostatoseminal vesiculectomy, was performed, including dissections of the pelvic lymph nodes en bloc. The method of diversion was ureteroileostomy. The postoperative course was uneventful.

Biochemical studies were within normal limits during the entire postoperative period. On June 11, 1954, the nonprotein nitrogen was 39 mg. per 100 cc., and the carbon dioxide 26 milliequiv. and the chloride 108 milliequiv. per liter.

Periodic intravenous pyelograms have demonstrated gradual return in function of the right upper urinary tract. One month after operation Grade 2 dilatation was noted. At the time of follow-up study, 1 year later, both upper tracts were pyelographically normal.

This patient had no evidence of pyelonephritis during his postoperative course. This is significant in view of the hydronephrosis that was present during the early period after surgery, a factor that frequently predisposes to infection.

Case 3. A 62-year-old man was admitted to the West Haven Veterans Administration Hospital on October 19, 1953, with papillomatosis of the bladder and prostatic urethra. He had had 11 transurethral fulgurations during the 4 years before the present admission. Physical examination was negative except for the cystoscopic findings. Laboratory work was within normal limits, including a nonprotein nitrogen of 35 mg. per 100 cc. and a carbon dioxide of 25 milliequiv. and chloride of 105 milliequiv. per liter. Intravenous pyelograms were normal.

A total cystectomy and prostatoseminal vesiculectomy with ureteroileostomy were performed on November 9. On the 8th postoperative day re-exploration was carried out for a small-bowel obstruction, the site of which was found to be a loop of ileum adherent to a raw surface in the pelvis. It was incidentally observed that the blood supply to the ileal loop was somewhat compromised by a hematoma at the base of its mesentery. On the 17th day after the original procedure, a urinary fistula developed. Re-exploration on January 20, 1954, revealed that the major portion of the ileal loop had sloughed. The ureteroileal anastomoses were intact and without evidence of stricture. After the ureters had been mobilized from scarred beds, a new ileal loop was prepared, and bilateral ureteroileostomy performed, again according to the prescribed technic. It was necessary to return the patient to the operating room 12 hours after this procedure because of a leak in one anastomosis, which proved to be the left. This anastomosis was repaired over a splinting catheter, which was left in place for 7 days as a safeguard against further leakage. Because of postoperative urinary drainage through the abdominal incision, a fistula was suspected from the right ureteroileal anastomosis, which had appeared intact at the time of surgery. This fistula was later demonstrated by x-ray study with the use of opaque materials. Because of a persistent urinary fistula, progressive hydronephrosis and repeated attacks of pyelonephritis, the right kidney was removed 4½ months after the original diversionary procedure.

At no time during the hospital course was there clinical or laboratory evidence of hyperchloremic acidosis. The patient was well 3 months after nephrectomy, with a well functioning ileostomy and 1 normal renal unit, as evidenced by intravenous pyelogram and phenosulfonphthalein excretion. Laboratory studies on May 17 revealed a nonprotein nitrogen of 36 mg. per 100 cc. and a carbon dioxide of 24 milliequiv. and chloride of 107 milliequiv. per liter.

This case illustrates the special care that must be taken to avoid torsion of the ileal loop or tension on its mesenteric attachment. It is also suggested that temporary splinting catheters should be used in cases in which the anastomosis is technically difficult or the blood supply to the ureter is in question, or when it is necessary to revise an anastomosis. If both ureters instead of only the left had been splinted with catheters at the time of reoperation, this patient might have avoided the development of the right ureteral fistula that subsequently necessitated nephrectomy.

Case 4. A 55-year-old man was admitted to the West Haven Veterans Administration Hospital on December 21, 1953, complaining of hematuria of 5 days' duration. Conservative operations had been performed on 3 previous occasions in attempts to control recurrent papillary transitional-cell carcinomas of the bladder. Surgery had consisted of a segmental resection in November, 1951, a transurethral resection in June, 1952, and a suprapubic fulguration in November, 1952. At the time of present admission there were no pertinent physical findings. Laboratory data were within normal limits, including a nonprotein nitrogen of 32 mg. per 100 cc. and a carbon dioxide of 27 milliequiv.

and chloride of 106 milliequiv. per liter. Intravenous pyelograms showed a normal left upper tract and a Grade 2 hydronephrosis on the right.

Transurethral observation and biopsy on December 23 revealed papillomatosis of the bladder and prostatic urethra. The right ureteral orifice was partially blocked. On January 5, 1954, a total cystectomy with prostatoseminal vesiculectomy and ureteroileostomy was performed. Convalescence was uneventful.

Laboratory data during the postoperative period were within normal limits. On June 8 the nonprotein nitrogen was 32 mg. per 100 cc., and the carbon dioxide 27 milliequiv. and the chloride 103 milliequiv. per liter.

Intravenous pyelograms after operation demonstrated a return of the right upper tract to normal in 30 days. Pyelograms have remained normal since that time. This patient has not had pyelonephritis since the procedure was performed.

CASE 5. A 55-year-old man was admitted to the West Haven Veterans Administration Hospital on January 19, 1954. He had noted progressive hematuria, frequency, dysuria and bladder spasm over a period of 4½ months. Physical examination was noncontributory except for evidence of recent weight loss. Laboratory data were within normal limits, including a nonprotein nitrogen of 25 mg. per 100 cc. and a carbon dioxide of 26 milliequiv. and chloride of 101 milliequiv. per liter. Intravenous pyelograms were normal. Transurethral endoscopy and biopsy revealed an extensive infiltrating transitional-cell carcinoma.

At operation on January 27 an inoperable carcinoma of the bladder was found. Because of distressing bladder symptoms, however, an ileal diversion was performed. The operative procedure was without untoward incident. On the 2d postoperative day the patient had a focal seizure followed by a generalized convulsion, from which he recovered without neurologic sequelae. The only abnormal chemical finding at the time of convulsions was a nonprotein nitrogen of 52 mg. per 100 cc. Urinary output was adequate. An intravenous pyelogram revealed 1 normal renal unit, and a Grade 1 (minimal) dilatation of the 2d. During the next 4 days the temperature ranged up to 105°F., seemingly out of all proportion to the physical findings. There was no evidence to substantiate a diagnosis of pyelonephritis.

The patient eventually recovered, and, by the end of the 4th postoperative week, pyelograms and all blood chemical values were normal. After several weeks of comfort and comparative good health, he deteriorated rapidly and died on March 27. Post-mortem examination revealed that the immediate cause of death was sepsis from a plastic peritonitis. This infection was secondary to small-bowel obstruction initiated by adhesions of the bowel to tumor implants.

The cause of the convulsions in the immediate postoperative period was unexplained.

CASE 6. A 62-year-old man was admitted to the West Haven Veterans Administration Hospital on February 15, 1954, complaining of malaise, back pain, anorexia and low-grade fever of 1 week's duration. Total cystectomy and ureterosigmoidostomy had been performed by the Cordonnier technic 3 years previously. He did well for 2½ years. During the 6 months before admission repeated bouts of pyelonephritis occurred in spite of several courses of sulfonamides and antibiotics. Attacks became more frequent and more severe.

Physical examination showed an alert but somewhat dehydrated man with marked bilateral costovertebral-angle tenderness. Biochemical determinations revealed a nonprotein nitrogen of 55 mg. per 100 cc. and a carbon dioxide of 14 milliequiv. and chloride of 117 milliequiv. per liter. On a regimen of forced fluids, frequent bowel evacuation, antibiotics and sodium bicarbonate, the carbon dioxide stabilized at 19 milliequiv. and the chloride at 114 milliequiv. per liter, and the nonprotein nitrogen fell to 45 mg. per 100 cc. Bilateral Grade 3 hydronephrosis was then noted by pyelogram.

Ureteroileostomy was elected as the procedure of choice to preserve the remaining renal function. Since operation, performed on March 1, the patient has done well. Laboratory data revealed normal nonprotein nitrogen, carbon dioxide and chloride values from the 2d postoperative day; 3 months after diversion the nonprotein nitrogen was 38 mg. per 100 cc., and the carbon dioxide 23 milliequiv. and the chloride 106 milliequiv. per liter. At that time hydronephrosis had been reduced to Grade 2 bilaterally. Pyelonephritis was not observed during the postoperative period of 11 months.

This case demonstrates that ureteroileostomy is feasible as a secondary diversionary procedure, and that it may be performed on patients on the brink of renal failure due to obstruction and infection. A group of patients whose prognosis might be considerably improved by ureteroileostomy as a secondary procedure would be the children with exstrophy of the bladder for whom ureterosigmoidostomy had failed. Such patients would have sufficient ureteral dilatation to make a mucosa-to-mucosa ureteroileal anastomosis technically feasible.

DISCUSSION

Table 1 presents the status of the individual renal units in our experience with ureteroileostomy.

TABLE 1. *Individual Renal Units.*

TYPE OF UNIT	ALL URETERS		NORMAL URETERS		HYDROURETERS	
	BEFORE OPERATION	AFTER OPERATION	BEFORE OPERATION	AFTER OPERATION	BEFORE OPERATION	AFTER OPERATION
Normal	7	9	7	6		3
Grade 1	1				1	
Grade 2	1	3		1	1	2
Grade 3	2				2	
Grade 4	1				1	
Totals	12	12	7	7	5	5

Pyelograms revealed that 6 of 7 renal units that were normal before diversion maintained normal pyelographic function afterward. In only 1 case in this group was there postoperative pyelographic evidence of hydroureter and hydronephrosis; this was the patient with the ureteral fistula who eventually required nephrectomy. The results in this small series are superior to the 51 per cent of normal values reported by Bricker.[26]

All renal units with evidence of obstruction preoperatively demonstrated varying degrees of improvement in the postoperative pyelogram. Three of the 5 units with preoperative obstruction returned to normal. One nonfunctioning unit showed gradual return of function, and was finally pyelographically normal a year after operation.

Pyelonephritis occurred in 1 of 6 cases — the patient with the urinary fistula.

Hyperchloremic acidosis was not noted in our series.

Bricker[22] has described in detail his technic of ureteroileal diversion. Several modifications of his method suggest themselves.

A left paramedian incision leaves the right lower quadrant free for placement of an ileostomy disk in the early postoperative period. The proximal ureteral

stumps are ligated early in the operation so that they will distend and thus facilitate the end-to-side, mucosa-to-mucosa anastomosis. It should be stressed that in the interest of preserving the blood supply to the ureter, a minimal length should be mobilized and that an ample quantity of periureteral tissue should be left attached to the ureter. Healing of the anastomosis is thereby encouraged. If the section of ileum selected for the loop is transected as close as possible to the ileocecal valve, exteriorization of its distal end can be accomplished with minimum tension. Occasionally, it is necessary to make a short transverse incision in the mesenteric border at the distal end of the ileal loop between the second and third arcades to facilitate exteriorization.

FIGURE 1. *Ureteroileostomy Drainage Apparatus* (A), *with Close-up of Ileostomy* (B).

In the performance of the ureteroileal anastomosis, a ureter of normal caliber should be slit along its anterior wall perpendicular to its line of transection to create a spatulate opening with a greater diameter for anastomosis. Bricker[22] has clearly described the details of this two-layered anastomosis; No. 00000 chromic catgut as interrupted sutures should be used for the inner layer, and No. 00000 silk for the outer. Particular care should be taken to tunnel the left ureter through the mesosigmoid without tension or angulation. Temporary splinting catheters may be used, as previously described, for difficult anastomosis, when the blood supply to the distal ureter is impaired or when it is necessary to revise an anastomosis. Indigo carmine may be injected intravenously at the completion of the anastomoses to demonstrate leakage. In exteriorization of the ileostomy the loop should be sufficiently redundant to allow the ileum to project about 2.5 cm. above skin level. In preparing a tract through the abdominal wall for the ileum, one should remove a button of tissue from all layers. Fascia is particularly prone to contract, and stenosis of the ileostomy may result if this precaution is not observed. To stabilize the loop, parietal peritoneum is sutured to bowel in several places with interrupted sutures of No. 00000 silk. Before closure of the abdominal incision, a No. 26 or No. 28 French catheter with multiple perforations is run down to within 1.5 cm. of the proximal end of the loop. Two purse-string sutures of No. 00 chromic catgut are placed in the distal end of the exteriorized ileal loop to stabilize the catheter and to prevent leakage of urine. The watertight seal thus created makes accurate measurement of urinary output possible in the immediate postoperative period and prevents soiling of the main incision. Bricker[27] has not been able to measure urine volumes in the early postoperative period because in the suturing of the mucosa of ileum to skin, there has been no satisfactory method of preventing leakage of urine into the dressing. The purse-string sutures that are placed in the exteriorized ileum cut through the bowel usually between the fifth and the seventh postoperative day. At that time an ileostomy apparatus previously described[28] is used to collect urine. A rubber body holder with a central perforation to admit the ileum is applied to the skin either with a two-faced adhesive disk or with skin cement. From the body holder a funnel-shaped latex sleeve leads to a short length of latex tubing, which in turn connects to a leg urinal (Fig. 1).

SUMMARY AND CONCLUSIONS

Ureteroileostomy is a method of urinary diversion consisting of transplating the ureters into a short isolated loop of small bowel. End-to-side anastomoses are performed by the mucosa-to-mucosa technic. This method shows promise of reducing the frequency of pyelonephritis and of preventing hyperchloremic acidosis.

Six cases in which ureteroileostomy was performed by this technic are reported. Of the renal units that

were pyelographically normal preoperatively, 6 of 7 (86 per cent) remained normal after diversion. All the renal units that were partially or completely obstructed before operation improved. No patient gave clinical or laboratory evidence of pyelonephritis or hyperchloremic acidosis.

Ureteroileostomy should be considered a worthwhile secondary procedure in cases in which other methods of diversion have been unsatisfactory.

Long-term follow-up studies will be necessary for accurate appraisal of this as well as other methods of urinary diversion.

References

1. Hinman, F., and Weyrauch, H. M., Jr. Critical study of different principles of surgery which have been used in uretero-intestinal implantation. *Internat. Abstr. Surg.* **64**:313-363, 1937.
2. Coffey, R. C. Physiologic implantation of severed ureter or common bile-duct into intestine. *J.A.M.A.* **56**:397-403, 1911.
3. Harvard, B. M., and Thompson, G. J. Congenital exstrophy of urinary bladder: late results of treatment by Coffey–Mayo method of uretero-intestinal anastomoses. *J. Urol.* **65**:223-234, 1951.
4. Nesbit, R. M. Ureterosigmoid anastomosis by direct elliptical connection: preliminary report. *J. Urol.* **61**:728-734, 1949.
5. Cordonnier, J. J. Ureterosigmoid anastomosis. *J. Urol.* **63**:276-285, 1950.
6. Cordonnier, J. J., and Lage, W. F. Evaluation of ureterosigmoid anastomosis by mucosa-to-mucosa method after 2½ years' experience. *J. Urol.* **66**:565-570, 1951.
7. Weyrauch, H. M., and Young, B. W. Evaluation of common methods of uretero-intestinal anastomoses: experimental study. *J. Urol.* **67**:880-891, 1952.
8. Woodruff, L. M., Cooper, J. F., and Leadbetter, W. F. Ureteroenterostomy: experimental studies. *J. Urol.* **67**:873-879, 1953.
9. Leadbetter, W. F. Consideration of problems incident to performance of uretero-enterostomy: report of technique. *J. Urol.* **65**: 818-830, 1951.
10. Mathisen, W. New method for ureterointestinal anastomosis. *Surg., Gynec. & Obst.* **96**:255-258, 1953.
11. Leadbetter, W. F. Unpublished data.
12. Ferris, D. O., and Odel, H. M. Electrolyte pattern of blood after bilateral ureterosigmoidostomy. *J.A.M.A.* **142**:634-640, 1950.
13. Lapides, J. Mechanism of electrolyte imbalance following ureterosigmoid transplantation. *Surg., Gynec. & Obst.* **93**:691-704, 1951.
14. Rosenberg, M. L. Physiology of hyperchloremic acidosis following uretero-sigmoidostomy: study of urinary reabsorption with radioactive isotopes. *J. Urol.* **70**:569-581, 1953.
15. Eiseman, B., and Bricker, E. M. Electrolyte absorption following bilateral uretero-enterostomy into isolated intestinal segment. *Ann. Surg.* **136**:761-769, 1952.
16. Brunschwig, A., and Lüscher, M. Hyperchloremic acidosis following anterior partial and complete pelvic exenteration. *Surgery* **35**: 197-203, 1954.
17. Foster, F. P., Drew, D. W., and Wiss, E. J. Hyperchloremic acidosis and potassium deficiency following total cystectomy and bilateral uretero-sigmoidostomy. *Lahey Clin. Bull.* **6**:231-238, 1950.
18. Matern, D. D. Hypokalemia accompanying hyperchloremic acidosis after ureterosigmoidostomy. *New Eng. J. Med.* **250**:941-944, 1954.
19. Bisgard, J. D., and Kerr, H. H. Substitution of urinary bladder with isolated segment of sigmoid colon. *Arch. Surg.* **59**:588-593, 1949.
20. Rubin, S. W. Formation of artificial urinary bladder with perfect continence: experimental study. *J. Urol.* **60**:874-906, 1948.
21. Thompson, H. T. Observations on isolated sigmoid loop substitution following total cystectomy in dog: preliminary report. *J. Urol.* **64**:85-101, 1950.
22. Bricker, M. Symposium on clinical surgery: bladder substitution after pelvic evisceration. *S. Clin. North America* **30**:1511-1521, 1950.
23. Boyce, W. H., and Vest, S. A. New concept concerning treatment of exstrophy of bladder. *J. Urol.* **67**:503-517, 1952.
24. Kinman, L. M., Sauer, D., Houston, V. T., and Melick, W. F. Substitution of excluded rectosigmoid colon for urinary bladder: preliminary report. *Arch. Surg.* **66**:531-537, 1953.
25. Gilchrist, R. K., Merricks, J. W., Hamlin, H. H., and Rieger, I. T. Construction of substitute bladder and urethra. *Surg., Gynec. & Obst.* **90**:752-760, 1950.
26. Bricker, E. M. Functional results of small intestinal segments as bladder substitutes following pelvic evisceration: progress report. *Surgery* **32**:372-383, 1952.
27. *Idem.* Bladder substitution with isolated small intestine segments: progress report. *Am. Surgeon* **18**:654-664, 1952.
28. Hurwitz, A. Original drainage apparatus for ileostomies and fistulas. *Surgery* **29**:463-465, 1951.

SPECIAL ARTICLE

LOVE: A CLINICAL DEFINITION

PHILIP SOLOMON, M.D.*

BOSTON

WHEN medical students ask the embarrassing question — "What is love?" — one is hard put to it to give a satisfactory answer. The term "love" is used in many different senses. A pediatrician will sometimes say that a querulous, ailing infant needs, among other things, "love" from a mother or mother figure. Gynecologists speak of women who "love" themselves so much that they avoid pregnancy because of what it may do to their figures. Surgeons and dermatologists know similar patients and the effect of scars and skin blemishes upon them. Internists and endocrinologists must reckon with their obese and diabetic patients' "love" of food and comfort. Urologists see the effects of a different kind of "love" when they work with venereal disease. The general practitioner in his role of family counselor may be consulted in matters having to do with "love" in the realm of infatuation and romance and their consequences. Surely the psychiatrist deals constantly with the vicissitudes of "love" of all sorts in his daily work.

*Clinical associate in psychiatry, Harvard Medical School; visiting psychiatrist, Boston City Hospital.

The word "love" is derived from the Sanskrit "lubhyati," meaning "he desires." It is true that desire seems to play a role in all meanings of the word, though it is a direct desire in some (food, comfort), implied in others (infatuation, romance) and vague or covert in still others (neighbor, country, mother). If one tries to define love in terms of emotional forces, desire by itself is inadequate. One might include elements of admiration, respect, idealization or even awe or fear; but at best, one might attain only a descriptive glossary that would add little actual meaning. Through the ages men have wrestled with the problem of love, particularly "romantic love," and in recent years psychoanalysis has thrown light on the subject.[1,2] This paper is an attempt to systematize current knowledge and to present it in a coherent way.

All love has a common origin, and the various forms of love differ only in the degree of abstraction, as expressed in dimensions, of the love object (Table 1). It is hoped that this formulation will reconcile the many uses of the term "love" in a unified con-

cept that will be of practical value to the medical student and physician.

Self-Love

To the newborn child the self constitutes the entire world. The primitive self-preservative instinct, the *élan vital,* the life force, Freud's "primary Narcissism,"[3] may be considered the basis of all love. Presumably, all living things display this instinct; even an ameba does what it can for itself. This force is one-dimensional: the location is always the self, and the only variable is the quantity or intensity. Higher forms of love are developments from this and are possible only in higher animals, the highest being present only in man. Even in man, the highest forms occur, as pointed out below, only in a limited number of men.

Primary self-love remains in some degree as long as one lives. It is still there at the deepest unconscious levels even when complex love structures of higher order have been erected and have taken on great importance in one's life. Evidence of it appears constantly in the satisfaction of basic instinctual needs — the deep breath, the full meal, the long drink, the joy of muscular activity. Sensuous pleasures generally fall in this category, and the aim is largely one of incorporation, to engulf and make the object part of one's self.

It may be noted that what is described here is not the same thing as selfishness, which implies an interest in the self to the exclusion of others, perhaps, indeed, with a callous indifference to others. Self-love may be present to a considerable degree and still be compatible with great consideration and affection for one's fellow man.

The disappearance or marked diminution of self-love is seen only in serious physical or mental illness. It is experienced as catastrophic feelings of utter annihilation, and it usually results in physical or mental death.

This type of love may be characterized as *love of me.*

Table 1. *Types and Dimensions of Love, with Some of Its Chief Characteristics.*

Dimensions	Type and Object	Meaning of Object	Additional Objects	Aim	Dynamics	Characteristic Expression	Psychologic Effect of Loss	Emotional Reaction to Loss	Distribution
One	Self	Me	None	Incorporation	Life force	Sensuous pleasures	Annihilation	Death	All life forms
Two	Projected self-love: Mother	What I am part of	Father; grandparents; nurse; minister; God.	Joining	Need to be cared for & protected & thus to stay alive	Cuddling; embracing.	Abandonment	Despair	Mammals
	Child	What is part of me	Creations; pets; possessions.	Adoration; cherish like myself; domination.	Reversing roles: acting toward child as one would like to be acted toward oneself.	Petting; beaming.	Mutilation; amputation; castration.	Horror; panic; fear.	Mammals
	Brother	What is like me	Friends; neighbors; countrymen; fellow man.	Sharing; companionship.	Sharing lightens burden & heightens joy	Hand shake; arm-in-arm.	Pain	Loneliness	Anthropoids; man.
Three	Romantic Ideal	What I should like to be	Hero	Identification	Ego ideal "attained" by loving one who credits me with it	Kiss; sex.	Anguish	Depression	Civilized man
Four	Maturity	What I should like to become	Professional, philanthropic & philosophic goals	Attainment; self-realization.	We strive together to approach future goals as close as possible	Enjoyable work; constructive effort.	Disappointment; grief.	Determination	Educated man

Case 1. A 27-year-old research worker in chemistry was referred for psychotherapy when his obesity failed to respond to repeated efforts at dieting and other medical measures. The patient had always been an excellent student and was now doing brilliant professional work.* However, he was socially shy and awkward; although he felt attracted by girls, he had had almost no experience with them. He was sensitive about his weight and yet could not reduce because of his love of eating. Psychotherapy extended over many months and revealed that his emotional development had been retarded by the lack of a strong father figure and by the excessive ministrations of the older sister who brought him up. At first, through identification with the therapist and later through healthy growth, he began to gain satisfactions from his interpersonal relations. By the time he was engaged to be married obesity was no longer a problem.

When the ability to love others is prevented by faulty child training, primary self-love becomes exaggerated, and social problems almost inevitably result.

Projected Self-Love

Here the self is still what is loved, but it is unconsciously conceived of as elsewhere and loved *there.* There are three varieties.

Love for the Mother

It is likely that the newborn baby, so far as he can feel at all, feels that his mother is part of himself. The breast, giver of sustenance, and the warmth of her body (or its substitute, the bed) are wonderful extensions of himself. When he first becomes aware that his mother can leave him, he *wants her back;* this yearning to be together again is called love for mother. It is understandable that this emotion is so strong since in early life so much of survival depends on it. The human infant would indeed perish if the mother, or some substitute for her, did not provide the requisite care.

The love for mother is rooted in the desire to be together with her again, a sort of next-best thing to being once more the entire previously safe and wonderful whole. The mother takes care of the child as though he were still part of her. Cuddling, embracing, drawing physically near are prominent characteristics of this type of love, since the aim is to join with the object. As the child grows older, the feeling is extended to other protecting figures: father, grandparents, nurse, cook, minister, God. Loss of the mother, particularly in those who have attained no higher form of love investment, causes wild despair and feelings of abandonment. The lost child feels that he will surely die.

This is *love for what I am part of.*

Case 2. A successful 36-year-old businessman made repeated visits to his family doctor with minor complaints. He was always in robust physical health. The patient, a bachelor, was devoted to his widowed mother, with whom he lived. The physician had several long talks with him and one with the patient's mother, finally suggesting that the patient take an apartment of his own in town so that he could be near his place of business. The mother decided on a prolonged visit to her sister in another state. The patient's symptoms disappeared and his social life expanded rapidly.

A constructive suggestion by the family doctor at the right time can act like a crystal dropped in a supersaturated solution.

Love for the Child

As the baby grows older he discovers his thumb, fingers, toes and other parts of his body; he realizes that they belong to him, and he treasures them. When appropriately used they can add to his pleasure; when injured they can make him suffer — they are part of him. Later, when he first becomes aware of other objects such as rattles, blocks and similar toys he naturally supposes that these are also parts of his body, and he usually tries to put them back by way of his mouth. Still later he becomes interested in his excreta, other possessions like clothes, dolls, pictures and pets, his own creations and eventually his own children. All these he cherishes and invests with considerable affection.

This type of love is again love for the self, but separated out and admired where it is. The aim is to take pleasure in the separated part (the child), to adore it, and to take pride in it. The parent loves the child in the way he wishes he could be loved himself. The characteristic gestures shown in this type of love are fondling, petting and stroking, associated with doting attention and a beaming gaze. Parents often use such expressions as "the apple of my eye," "my right arm" and "such a part of me." Loss of this type of love object is experienced as loss of an important part of the body, a mutilation, and the emotional response is one of acute panicky fear and horror.

Many lower animals, particularly mammals, give indications of love reactions between the parents and their young, though most of what one sees can be accounted for on the basis of protective instinctual patterns. In man, the relation persists and remains meaningful after the maturation of the young. It should be added that in both love for the child and love for the mother certain prohibitions are operative in contemporary society. Incest taboos and fear of the parent of the same sex are prevalent, so that expression of love between parent and child is limited and often seasoned with a touch of danger.

This type of love is *love for what is part of me.*

Case 3. A 60-year-old man was met through his daughter, who had undertaken psychoanalysis. She was unable to bring herself to marry in spite of many presentable suitors. She had 5 older brothers, none of whom were married or self-supporting. The father, a former immigrant, was a self-made man who found time to concern himself with every detail of his children's lives. He sighed and deplored their lack of "success," but resisted powerfully any move they made toward leaving his bounty. His wife had had several psychotic illnesses.

The exaggeration of this type of love may inhibit the normal emotional maturation of children. Mother love can become "smother love."

Love for a Brother

As the child grows older he may notice others like himself, small, relatively helpless and taken care of by the same parents. His feelings toward these siblings will be mixed: toward the older ones he may attempt to relate himself as to his parents, for additional protection and care; toward the younger ones he may to some extent play the role of parent himself as though to show the real parents how he would like to be treated; toward both, and especially toward a twin or sibling near in age, there may be rivalry, jealousy and antagonism. Only later a new feeling may arise, one of partial identification, a sharing. It has been said that sharing halves one's sorrows and doubles one's joys. Certainly, the ability to share involves a stretching of one's ego boundaries to take in, at least at some levels and symbolically, the egos of others, a process entailing the willingness to give as well as to take.

This type of love extends from siblings to those who are like siblings; depending on the mental and emotional capacity of the individual it may encom-

pass friends, neighbors, countrymen and one's fellow man generally. Some animals, especially anthropoids, seem capable of rudimentary forms of this love, but its real development is in man; because of the competitive elements, it is characteristically ambivalent, contingent and capricious. It can be recognized by its "Platonic" aspects — the hand-shake, arm-in-arm, pat-on-the-back relation of companions. The loss of this love object is felt as various degrees of pain and suffering and results in loneliness.

This is *love for what is like me.*

CASE 4. A 10-year-old girl was referred to a child-guidance clinic by the school authorities because of bullying and unruly behavior. She had 2 older sisters and 2 younger brothers. She felt excluded from both her sibling pairs, who seemed to get along very well without her. During treatment she formed a strong attachment to her therapist. She was helped to go to a summer camp and to join a play group of girls of her own age. She became much more affable and often repeated what the therapist had told her: "The best part of a sandwich is in the middle."

Many persons (perhaps all) find giving difficult until they have experienced sufficient taking.

In projected self-love there are two dimensions or degrees of freedom: the intensity of the feeling and the direction in which it is expressed. The latter may be thought of as a displacement from the self along a line leading in one direction to mother, and in the other, to child and brother.

IDEAL-SELF LOVE

The young adolescent becomes educated, is influenced by the culture of civilized society and develops ambitions and goals that constitute his "ego ideal." Usually, it is not long before he realizes that he falls short of his standards. The mature adult, when he finds himself in this predicament (which is most of the time), reacts by some combination of renewed efforts to reach his goals and acceptance of the fact that he has not reached them. The adolescent is more apt to react with discontent, restlessness and depression.

There are several remedies open to him, depending on his imagination, courage and initiative. The simplest is to seek solace in romantic and adventurous movies, television, radio, books and magazines; he "is" the omnipresent hero, famed for feats of derring-do, and there is quick, though temporary, surcease to his suffering. More difficult, but of longer duration, is the choosing of a living hero to worship: a football or baseball idol, a five-star general, the school athletic coach or even a big brother or father. "Crushes" on teachers, camp counselors and group leaders are familiar at this time. A little direct contact with the idolized hero helps enormously. Running an errand for the teacher means sharing the teacher's life a little, which facilitates identification with the teacher. Usually, it is not long before these efforts to be someone other than himself also fail to satisfy.

A new phenomenon may now appear: the boy "falls in love" with a girl. What happens? The girl regards him as the very same hero he has been wishing he were! He accepts her verdict and adores her for it. The affair is reciprocal: she in turn sees in his eyes the girl she has been yearning to be, and they dote on one another. A crossed identification takes place[4]; regarding their judgments of one another each adopts that of the other, and gladly since it happens to correspond to what is wished for but despaired of in himself. The result is an *infatuation,* characterized by marked overevaluation of the love object. The boy thinks he loves the girl; what he loves is the idealized version of himself that she sees in him. When he is with her he can believe that he *is* the idealized self that he wishes he were.

The phenomenon of infatuation is the basis of romantic love. It is evident from the discussion above and from derivative considerations that several conditions are necessary before it can come about:

In the first place there must be an appreciable discrepancy between the actual self and the ideal self. In societies where ambition and competition are at a minimum, romantic love is virtually unknown. In the present highly competitive modern civilization, full of ever-increasing standards and further-reaching goals, romantic infatuation, with its sequelae of poorly chosen marriages, divorce and broken homes, has become a serious problem.

Secondly, maturity of personality must be lacking, else the person will find realistic ways of dealing with the problem of his ego-ideal. It is no accident that infatuations in early adolescence, when emotional maturity is still far off, are almost the rule ("puppy love") whereas infatuations in later life predominate in emotionally unstable persons and are more common at times of particular stress such as the menopause ("the foolish forties").

Thirdly, the sense of reality must be capable of being put in abeyance. Love is notoriously blind; the infatuate must be oblivious to the overevaluation that he practices on his love object and she practices on him in return, since these circumstances are necessary for the phenomenon of infatuation to occur. Thus, when realistic judgment returns, the infatuation collapses. (No doubt this is one reason, though not the only one, why lovers prefer poetry to prose and the unreal glow of moonlight, or candle-light to the harsh reality of the sun.) It is with good reason that the lover is compared to the inebriate and to the psychotic ("drunk with love" and "mad with love"), since infatuation, intoxication and insanity have one important element in common, the dissolution of the reality sense.

Fourthly, the infatuation must be reciprocal. Since *being loved* is the essence of infatuation, it cannot occur unilaterally. However, in the unconscious, an imagined emotional force may be as important as a real one. The boy who fancies that the girl loves him or that she will soon love him is in just as strategic a position to develop an infatuation as the boy who receives every evidence of his girl's love. Un-

requited love of this type can indeed exist for a short time but only because in fantasy it is not unrequited. Infatuation is completely incompatible with the reality of genuine rejection.

Fifthly, the girl must possess some attributes in reality that the boy finds attractive; otherwise, he could not value her judgment or identify himself with her. The particular features that are necessary depend on the boy's state of mind (and on the characteristics of the mother, sisters and other meaningful women in his life experience). In early adolescence the girl's ability to act as though she were poised and sophisticated is important to the boy. A little later the sexual aspects of dress and figure become more prominent. Still later the girl's actual behavior, physically, intellectually and emotionally, come into account. Only rarely, and then in the nearly mature man, is the full personality and being of the woman considered. But the attributes that have just been mentioned are merely necessary, not sufficient, conditions for the infatuation. The boy meets many girls at various times who attract him, and only with a special girl at a special time will he become infatuated. The other conditions mentioned above must also apply: he must be depressed and to some extent immature and unrealistic, and the girl must be considered as reciprocating. When all the conditions are operating the infatuation may occur almost instantly ("love at first sight"), and if any *one* condition ceases to operate the infatuation may as rapidly vanish.

Finally, the degree of unconscious fixation on the mother can be neither too great nor too little. If it is too great, no other woman will be able to replace, even partially, the mentally built-in mother figure. If it is too little there will be insufficient attraction toward any woman. Instances of the former are seen in bachelors who live with their indulgent mothers (as in Case 2, discussed above) and insist that they would get married if they could only find the right girl. Instances of the latter are overt homosexuals, who perhaps had overbearing, fearful mothers whom they could not love. Most men fall comfortably in between; such femininity as is present in them remains latent, but can find unconscious expression in the identification with the girl that takes place in the infatuation.

Romantic love, glorified in song and story across the centuries, is a relatively new phenomenon in the history of mankind. It became most prominent at the time of the troubadours in the eleventh century. Even today it is virtually unknown in parts of the Orient and among great masses of the world's population. Those that are capable of it must have the imagination to conceive of their ideal so vividly as to be able to "create" it in the eyes of the beloved. The power of symbolization and abstraction that is involved is different from that of the other forms of love already discussed. The variables of intensity and projection are present as before, but now there is the new element of what *might* or *ought* to be, as distinguished from what *is*. Thus this is three-dimensional love. Its characteristic mode of expression is sexual. The loss of the love object is felt as anguish and results in deep, but temporary, depression.

This is *love for what I should like to be.*

CASE 5. A 48-year-old respectable family man, with a devoted wife and 3 fine children, had fallen in love with one of his employees, a girl of 29. He could not bear to hurt his wife, who had worked hard at his side through all their years of struggle. Yet he could not resist the overpowering effect of the girl's physical attraction and of her obvious adoration of him and dependence on him. He talked endlessly to the psychiatrist of the utter impossibility of deciding either way and of the increasing difficulties in attempting to hold on to both women.

After several months of tortured existence he finally realized that he was the victim of an infatuation. It had begun at a time when his business was doing poorly and he had lost a long-cherished ambition. He had begun to think that he was "slipping," that he was growing old, and he noted with dismay the graying at the temples and his flagging interest in sex with his wife. It was at this point that fortuitous circumstances — the girl's touch of flirtatiousness and her sincere and unbounded admiration of him — had combined to bring about his undoing. He had felt rejuvenated, reprieved and regenerated; by being loved he could love himself again.

Through the increased ego strength that he acquired during the course of psychotherapy, the patient became less dependent on outside support, from his mistress and from his wife also. When he saw how his relation with the girl was increasingly jeopardizing her chances in life he finally allowed her to accept a position in another city, where she subsequently married. With his wife, he gradually developed a deeper and more meaningful union. His friends and business associates noticed the signs of his growing maturity.

It is useless to argue with the infatuate. He will not change unless he succeeds in growing to greater maturity through psychiatric help or through the hard knocks of reality.

MATURE LOVE

A young man in high school and college has several infatuations, and in professional school one or two more-mature love affairs. Finally, he finishes his education, becomes self-supporting and marries. He and his wife love one another intensely almost from the start. With marriage, the love seems to grow even greater.

This love does not last. The stubbornest overevaluation dissolves under the slow drip of reality; the strongest infatuation erodes when exposed to the heat and cold, the tears and frost of marriage weather. Even sex loses some of its appeal; it is no longer so forbidden or novel, and the excitement of conquest is diminished. Two people remain, stripped of pretense, joined together in a sociolegal enterprise with variable assets and liabilities. The former include the possession of a partner in the business of life, one with whom much that is good may be shared. The latter involve duties and responsibilities to the spouse and to such children as may have resulted, as well as restricted behavior to the rest of the world. The fate of the marriage hinges on the emotional relation between the two partners.

A wife represents three things to a man: a mother, a daughter and a mistress. Similarly, a husband serves as a father, a son and a lover. In the best marriages the lover-mistress roles predominate, with companionship and friendship as abundant corollaries. When the husband wishes to be a son, the wife is willing to be a mother; when she wishes to be a daughter, he will play father. The patience, tolerance and flexibility between the two are the determining factors.

In poor marriages the two may not have enough in common in the way of sense of values and general outlook to be successful partners. The ties that bind them are then based essentially on neurotic scripts, and these are notorious for their propensity to frequent changes in the cast of characters.

CASE 6. A 36-year-old woman was having difficulties in her 4th marriage. Her husband, in his 3d, admitted that he was being unfaithful, but blamed his wife and her constant nagging. Both were intelligent, successful, professional people who had entered this marriage with high hopes of permanent happiness. In the course of psychoanalysis, it became clear that this woman was seeking the kindly father who adored her when she was a child, but who died when she was very young. Her husbands were older men who similarly adored and protected her until she began to vent on them her spite and bitterness. These negative feelings occurred at the slightest separation or threat of separation and were shown to be related to her fear of again being abandoned as she was by her father when he died.

In good marriages when romantic love has sung its brief song, a soberer and wiser couple remain, disillusioned and perhaps a bit grim, but not defeated. The two are now ready to learn how a marriage must be worked at to make it a success; they will utilize all their resources to make the partnership a going concern. They will be thankful for whatever kind of love is still left to them: parental and companionable, and their own self-love, which they will not spurn. Sex will not be the thrilling adventure it once was, but it will still be gratifying. They will be satisfied with this and not seek new partners with whom to attempt to rediscover the old thrill, and its inevitable chill. Such a marriage, in spite of the loss of romance, — indeed, because of it, — can become constantly better and more rewarding. Children may be born and grow up and leave, and the husband and wife still share all this too as their lives intertwine and intermingle.

For a few, the kind of love that evolves from such a relation transcends any that has been experienced before. The sharing is more than that of brother and sister; the most intimate goals and ambitions are striven for jointly; pleasure, suffering and work are experienced mutually. The identification of interests and aims extends to the highest levels and to the most distant future; professional, philanthropic, philosophic and spiritual values are interchanged and welded together. Both may share deep religious convictions, or both may feel that there is no ultimate truth and no absolute good, no complete maturity or perfect wisdom, no utter happiness; what they strive for then is to approach these ends as closely as possible, to realize their collective potentialities and to fulfill themselves together. This is love of a different sort; it involves an ideal, as in romantic love, and thus partakes of the same three dimensions (intensity, projection and idealness), but also transcends the "here" and "now" to involve the future. Time, the new degree of freedom, makes this love four-dimensional.

This type of love is farthest removed from the primitive bodily functions and dependent to the fullest extent on the phylogenetically most recently developed cortical functions. Here, one must be dealing with the educated man; here, the expression of love is in constructive working, planning and living together; and here, in a sense, there can be no loss of the love object. A man's wife may die and the man will suffer deep grief, but the ideal toward which both have been striving lives on. In continuing to work for it the man finds his wife's influence is still there with him and can never be lost; he can carry on with renewed determination.

This is *love for what I should like to become.*

DISCUSSION

There are three primary colors, but color that occurs in nature is usually a mixture of these. Human love is also apt to be a mixture. Typical is a mother's love for her son. Much of the time, as when she watches him sing in the church choir or beams at his good report card, she feels mother love, but when he helps her with the dishes or in cleaning up the cellar she feels more the companionable warmth of sister to brother; and when she notices how much he looks like his father or her father, and when he gives her an enthusiastic hug, or sits on her lap, her feelings may be still different, though perhaps this time partly or wholly repressed.

The love of a husband for his wife has already been referred to in its complexity. He may love her as a mother, a daughter, a sister, a mistress or as his "ideal," and sometimes he may share with her a truly mature love. These various loves are by no means mutually exclusive; they overlap and intermix and change from time to time, even from moment to moment, with the variety and profusion of the kaleidoscope.

What has just been said about the love of mother and son and husband for wife is similarly applicable to other human loves: teacher and pupil, friend and friend, doctor and patient.

Where does sex fit into the picture? Everywhere or nowhere, depending on one's definition of it. If one considers it as Freud did, it is equated to all life force or libido, and all love is merely a form of it. If one thinks of it strictly as a genital and endocrine function it is found to be frequently associated with certain forms of love, infrequently associated with others and really irrelevant to all (except for its par-

ticipation in bodily self-love). Certainly, sex in its sensuous aspects contributes greatly to instinctual gratification; when linked with the spirit of conquest and the excitement of novelty and wrongdoing it becomes an important element of romantic love; when it is a part of a true life sharing it has its place in mature love. A similar case could be made for eating. All the instincts go to make up the life force of self-love and are thus part of the root of all other loves, but their individual manifestations in connection with other loves are variable and in fact often culturally determined.

Finally, a word should be said about giving and taking in the love relation. It has been said that love should be thought of as an "overflow," as from a vessel filled beyond the brim with the goodness of life. Where would such an attractive concept fit into the dimensional analysis elaborated here? If all love is a derivative of self-love, it is easy to see the taking, but where is the giving? The answer is that the giving is basically giving to the self. The government servant who works loyally for his country conceives of his country unconsciously as the mother that he is part of; he thus works for himself, since he identifies himself with anything he is part of. The mother who gives love to the child gives it as though the child were part of herself, perhaps the most precious part. The soldier who sacrifices his life for his buddy does it as though his buddy were the better part of himself. The romantic lover gives abundantly of his love, but to the representative of his own ideal of himself. Even in mature love, the partners share in giving love to one another and to their life work as though they were giving to their eventual idealized selves. The distinction between the one who loves freely and the one who loves niggardly thus resolves itself into the matter of the ease with which a person can identify himself with other persons, or with concepts. The loving person readily extends his ego boundaries to include others; the unloving person constricts his ego and is reluctant to allow anyone in. The confident, empathic person will love fully and widely; the insecure, unimaginative person will be incapable of loving.

Summary and Conclusions

In an attempt to systematize understanding of the concept "love," as utilized in many ways in clinical medicine, the subject is considered from the standpoint of dimensional analysis in terms of the degree of abstraction of the love object. Primary, or one-dimensional, love is self-love, the source of all other loves. Two-dimensional love involves unconscious projection of the self elsewhere and loving it there: mother, child, brother. Three-dimensional love is romantic love for one's ideal self. Four-dimensional love is mature love that strives toward an eventual ideal.

References

1. Freud, S. Contributions to psychology of love. In *Collected Papers.* Vol. 4. 508 pp. London: Hogarth, 1925. Pp. 192-217.
2. Balint, M. On genital love. *Internat. J. Psycho-Analysis* **29**:34-40, 1948.
3. Freud, S. On narcissism: introduction. In *Collected Papers.* Vol. 4. 508 pp. London: Hogarth, 1925. Pp. 30-60.
4. Reik, T. *Psychology of Sex Relations.* 243 pp. New York: Rinehart, 1945.

MEDICAL PROGRESS

SYPHILIS (Concluded)*

Robert F. Tilley, M.D.†

Brookline, Massachusetts

Therapy

The worth of penicillin as an agent for the management of all types of syphilis has been established. The end results of intensive follow-up studies have confirmed the initial impressions of the conservative syphilologists. Penicillin is the drug of choice because of its ease of administration and nontoxicity. Retreatment should be instituted in the face of an obvious clinical relapse or progression. Serorelapse should also be considered an indication for further therapy. These failures can only be determined by the proper observation of the patient. Once treatment is instituted the patient must be followed and all the persons known to have been exposed to the patient must be investigated. If the private physician is capable of assuming the treatment of the individual patient he must also assume the responsibilities.

Penicillin is adequate by itself without the addition of the older heavy metals. The opinion of several leading syphilologists is that with penicillin therapy the clinical failure rate will be approximately 5 per cent and the cure rate close to 90 per cent.[37] In primary and secondary syphilis the initial injection should consist of 2,400,000 units, and this should be followed by 600,000 units every four days for four doses. Six million units of penicillin in divided dosage should be given over a ten-day period in latent syphilis; 6,000,000 to 12,000,000 units will be necessary to treat neural and cardiovascular involvement. In the presence of pregnancy 4,800,000 units should be given if the diagnosis is made during the first six months. After that the dose should be 600,000 daily for eight days. If the patient is already in labor 2,-

*From the Department of Dermatology and Syphilology, Harvard Medical School and Massachusetts General Hospital.

†Assistant in dermatology, Harvard Medical School; assistant dermatologist, Massachusetts General Hospital.

400,000 units should be given immediately and repeated in a week. Early congenital syphilis should be managed by the administration of 10,000 units of penicillin per pound of body weight daily for ten days. Late congenital syphilis requires 6,000,000 units. All the programs mentioned above can be followed with the patient reporting for the injection daily. Inpatient care is not needed but may be desirable with certain clinical problems.

Early Syphilis

Recent reports have dealt mainly with penicillin therapy and its results. The various long-acting types of penicillin have been investigated. Single injections of procaine penicillin in oil with aluminum monostearate were employed in a series of 124 cases of secondary syphilis.[38] The drug, in a dosage varying from 1,200,000 to 4,800,000 units, gave a serologic cure in 73 per cent. Retreatment was necessary in 13.7 per cent. The series was too small for valid conclusions, but the results suggest that this form of therapy may be adequate. Another study utilizing N,N′ dibenzylethylenediamine dipenicillin G demonstrated the efficacy of this drug.[39] Impressive blood levels and good clinical results were obtained with 2,500,000 units. Among 127 patients treated and followed for twelve to fifteen months the serologic response was good, with a 90 per cent seronegativity rate; 5 per cent required treatment.

In a series of 409 patients requiring retreatment because of persistence of seropositive reactions after the initial schedule of penicillin therapy 81 per cent attained seronegativity.[40] This is not too good a result, but even those still positive will eventually become negative since it is known from past studies that, with a low titer of positivity and normal spinal fluid, the blood will become negative one or more years after treatment, provided reinfection and relapses do not occur. Furthermore, the data show that the so-called poor results from penicillin were those seen during 1943 - 1947, when the drug was still unstable. Since 1947 the failure rates at Bellevue Hospital have been well under 10 per cent.

Another observer believes that the failure rate is probably less than 5 per cent if one interprets the majority of cases reported as relapses and seroresistant cases as reinfection.[41] The difficult criteria for establishing a true reinfection are reviewed critically, and the ease with which patients are categorically considered failures discussed. Some of these failures could be reinfections without lesions and without change in the serologic titers; others might be biologic false-positive reactions developing after the initial cure.

Neurosyphilis

Various reports have evaluated the results of penicillin in neurosyphilis. In a group of 130 paretic patients an attempt was made to determine the net gain by showing the percentage that had returned to the community.[42] These patients had had their disease an average of twenty-two months, and had all received conventional therapy, the penicillin dosage varying from 3,000,000 to 9,000,000 units; 42 per cent were discharged, 49 per cent remained in the institution, and 9 per cent died. The work level of those returned to the community varied a great deal. The best results were obtained in those with a rapid onset of symptoms and those with symptoms of short duration. Again, in a series of 469 patients followed for one to six years, the results were good in that 58 per cent showed clinical improvement, 56 per cent were gainfully employed and 56 per cent had made a good or fair social adjustment.[43]

Malaria in addition to penicillin added nothing to the final outcome in a group of patients similar to a group treated with penicillin alone.[44] New physical signs did not follow penicillin therapy. Retreatment did not accomplish more improvements. In a group of 639 patients 430 were adequately followed for one to five years.[45] Penicillin treatment was used in 51 per cent, and penicillin and malaria in 49 per cent. The results were the same so far as clinical improvement and ability to work were concerned. The few patients who died and were autopsied gave little evidence of syphilis.

In another series of 603 patients with varying types of neurosyphilis it was noted that the spinal-fluid response was most rapid during the first year.[46] Spinal-fluid relapses occurred after the third or fourth year in paresis and tabes. Repetition of treatment was followed by only slight improvement in 3 to 5 per cent. In another analysis of 388 patients with neurosyphilis 3 were repeatedly treated because of continued evidence of activity in the spinal fluid.[47] Two of these finally reached an inactive stage as a result of a final course of therapy employing 30,000,000 units of penicillin.

In asymptomatic neurosyphilis 10 out of 112 patients still had an abnormal spinal-fluid cell count at the end of six months.[48] This suggests that the spinal fluid must be checked periodically even though penicillin is a superior drug. A follow-up study of blood and spinal-fluid tests for reagin after the treatment of neurosyphilis disclosed that the blood test remained positive for ten years in 70 per cent and the spinal fluid in 27.7 per cent.[49] Retreatment had no effect in reducing strongly positive tests. Relapse of neurosyphilis, as determined by an increase in the spinal-fluid cell count, never occurred later than two years after treatment had inactivated the infection.

Autopsy studies in 6 out of 7 patients in whom penicillin therapy was given for neurosyphilis showed such complete clearing of the inflammation that the diagnosis of syphilis might be doubtful.[50] One paretic patient who died three weeks after treatment still showed the usual type of inflammatory change.

Penicillin has been effective in controlling progression in some cases of optic atrophy, but it cannot im-

prove the visual acuity.[51] The critical level of visual acuity is 20/50, and any patients with this level or better can expect satisfactory arrest of their disease.[52]

Cardiovascular Syphilis

The great fear of reactions to penicillin such as the Jarisch–Herxheimer reaction and the therapeutic paradox has been dispelled. In a series of 111 cases there was no indication of either, and definite relief of anginal pain occurred in 4 out of 5.[53] Improvement was gained in 33.3 per cent of the cases of simple aortitis and 64 per cent of those of aortic regurgitation. Aneurysms were too few to permit evaluation. Penicillin had no effect on the serologic tests in the series of cases. A larger group of patients followed for a period extending from one to sixty months showed similar results.[54,55] Of the 167 patients with aortitic insufficiency and 11 with saccular aneurysm 30 per cent also had neurosyphilis. Again, there was no reaction to the therapy, which was thought to be safe. In another report 21 cases of cardiovascular syphilis previously untreated were managed with penicillin, with no untoward reaction.[56] A further study has demonstrated the value of therapy in 334 cases.[57] The earlier treatment was instituted, the more effective it was, and the better the prognosis.

Ocular Syphilis

Involvement of the eye occurs both in acquired and in congenital syphilis. Modern penicillin therapy can prevent the ocular manifestations, but once the scleras are scarred and the optic nerve blanched treatment is relatively ineffectual. There are at present in the United States 262,000 persons adjudged to be legally blind, and syphilis is responsible for 10 to 15 per cent of this number.[58] Thus, it approaches cataract and glaucoma as a cause of blindness, and since simple methods of prophylaxis exist it certainly merits as much attention.

Primary optic-nerve atrophy is seen in 10 to 15 per cent of acquired and in 50 per cent of congenital tabes. Early diagnosis depends on awareness of the condition. Pupillary abnormalities, which are the earliest and most constant signs of neurosyphilis, may precede by years the appearance of subjective symptoms. Interstitial keratitis is a less common cause of blindness, occurring in varying degrees of severity in 30 to 50 per cent of congenital syphilitics. Once a diagnosis of neurosyphilis is established ophthalmoscopic and perimetric examinations are essential.[59] Early optic atrophy may be found even with negative spinal-fluid and blood tests. Once the optic disks are pale the condition is beyond help. Treatment in the early stages prevents progress of the optic-nerve atrophy and thus preserves visual acuity.

Analysis of figures from a single state shows that in a ten-year period a total of 6442 persons were considered legally blind and the exact diagnosis was listed in 2427 of them.[60] Infectious diseases were at fault in 852, the infection being syphilis in at least 50 per cent. On further study it was noted that although a reported decline in mortality, psychoses and cardiac disease had been attributed to syphilis, no such appreciable decrease was discernible in the annual rates of blindness from that cause. Since there is an average of seventeen years between infection and blindness there is more than adequate time to diagnose and prevent this complication. More emphasis must be given to case finding and diagnosis. Premarital and prenatal screening by serologic testing, which covers only isolated episodes in a person's life, should be supplemented by some other serologic survey.

The higher rate of interstitial keratitis at puberty and its exclusive appearance in congenital syphilis has provoked much thought for many years. The frequent finding of syphilitic involvement of the endocrine glands in stillbirth due to congenital syphilis has also implicated the possibility of an underlying endocrine disease as the cause of interstitial keratitis. A clinical study of 145 patients with interstitial keratitis suggested some suppression of androgens or an imbalance between estrogens and androgens.[61] A further laboratory survey of 42 of these patients, including determinations of the basal metabolic rate, protein-bound iodine, serum sodium and potassium, radioiodine-tracer studies and urinary 17-ketosteroids, glucose tolerance test and eosinophil test, implicated an underactivity of the thyroid, pituitary and androgenic function as a factor in the development of interstitial keratitis due to syphilis.

The local use of cortisone has been followed by great improvement in some cases of interstitial keratitis. In one series of 11 cases all but 1 patient had received adequate routine treatment for the syphilis including arsenic, bismuth, penicillin and, in 5 of the 11, fever therapy.[62] Seventeen eyes were involved; 11 of these showed vascularization, and 6 were infiltrated. Treatment consisted of more penicillin and the instillation of a 2.5 per cent solution of cortisone. Therapy was stopped at the end of ten days. After four days the photophobia, lacrimation and blepharitis were relieved. The progress of the keratitis was controlled if not arrested at ten days. Six of the eyes not vascularized healed without vascularization. In some cases it was necessary to repeat the treatment a second time, and in 2 cases there were three separate courses of therapy. The over-all results were excellent, but the period of observation is too short to determine if this is a permanent effect. Another observer noted inconsistent results with cortisone eye solution in interstitial keratitis.[63] The therapy was most effective in early stages of edema and cellular infiltrate and less so in abnormal cases of vascularization with necrosis. Recurrences followed termination of instillations, and 3 of the patients described were still using the local cortisone solution after five months.

Prevention of Congenital Syphilis

The data assembled thus far show that penicillin therapy in pregnancy is almost 100 per cent effective in preventing congenital syphilis. The ease of its use, the absence of toxicity and its effectiveness even late in the third trimester have been a boon to the obstetrician, the pediatrician and the syphilologist. In the presence of a confirmed positive blood test in a pregnant woman without confirmatory past history of syphilis and with no clinical evidence of disease, a decision about the institution of antisyphilitic treatment is no longer so difficult. Penicillin can be given without fear of toxicity to the mother, and it promises to rid the possibly infected fetus of all dangers. A hasty diagnosis is never condoned, but the birth of a single congenitally infected infant is to be condemned. Once the post-partum period is concluded the clinician can approach the problem with more time and no fear at his disposal. Some erroneous diagnoses may be made and can never be retrieved, but such mistakes are excusable when a possible single case of congenital syphilis is prevented.

A large series of pregnant women known to be infected with syphilis were followed closely. In 1002 cases a total of 10 infants in whom a diagnosis of congenital syphilis was established were delivered. Of these, 5 were living, and 4 stillborn, and there was 1 neonatal death.[64] The 1 neonatal death and the 4 infections in living children were due to either infectious relapses or reinfection in women who were lost from observation during the latter part of pregnancy. In view of this it is believed that once adequate penicillin therapy has been completed and the blood test remains negative or weakly positive no further treatment is needed in pregnancy. If, however, the blood test is positive and the patient is unco-operative, retreatment is advisable. Furthermore, the presence of a positive serologic test for syphilis on umbilical-cord blood does not indicate the need for therapy. X-ray evidence of osteitis of the long bones likewise does not indicate the presence of active disease in the infant.

An analysis of the incidence of congenital syphilis in Baltimore disclosed that despite improvement in case-finding technics there has been a decline in the morbidity of congenital syphilis.[65] In 1936 the peak of 154 per 1000 nonwhite infants was reached, and this had declined to 2.33 per 1000 in 1950. A study of 34 cases of congenital syphilis was undertaken to determine if possible why these were not prevented. In 17 there was no prenatal care, and 2 mothers had received prenatal care only during the last week. Four patients had the infection or a relapse late in pregnancy. In 6 the fault rested with the medical agencies responsible, since the presence of infection was known but not treated. Finally, 2 infants diagnosed and treated for congenital syphilis probably were not infected. None of these cases would have been prevented by any type of law requiring prenatal blood tests. A point may be reached eventually where no further reduction in morbidity will occur except coincidentally with a decrease in syphilis in pregnancy.

Special Problems Produced by Penicillin

This subject does not include the well known allergic reactions to penicillin, nor does it refer to therapeutic paradox nor to the Jarisch–Herxheimer reaction. With the simplification of antisyphilitic therapy certain misconceptions soon appeared. Some of these have been perpetuated in the literature. A worthwhile summation of these diagnostic and therapeutic pitfalls emphasizes certain salient points that bear repeating. The physician's paramount responsibility after the institution of therapy is to ensure not only that the treatment is completed but also that the patient returns for necessary follow-up observations.[66] A diagnosis of congenital syphilis cannot be made solely because of a positive blood test. There must be clinical lesions on which a dark-field examination is positive. Passive transfer of reagin from mother to fetus may result in a weakly positive test in the infants' blood for three months.[67] In congenital syphilis the blood test may be negative or weakly positive from four to twelve weeks of age and should then become strongly positive.

Another problem is that of seroresistance after penicillin therapy. The decision for retreatment is a difficult one. The effect of retreatment, moreover, is not striking. In a group of 693 patients treated for primary syphilis the serologic tests were still positive in 3.5 per cent after a year. In 18.2 to 32.6 per cent of those treated for secondary syphilis the tests were still positive. Further therapy had little or no effect on the positive blood tests. Prolonged seroresistance in the absence of relapse, reinfection or progression does not mean continuance of syphilitic infection.

X-Ray Studies

Angiocardiography has been employed in 93 patients, 83 of whom had late syphilis.[69] The relative merits of physical examination, x-ray study of the chest and angiocardiography were compared. Angiocardiography alone established the diagnosis in 15 cases, sustained it in 17 and excluded it in 9. The presence of an aortic systolic murmur and the prolonged ringing second aortic sound was of relatively little value in establishing a diagnosis of early aortitis.

A study of the skeletal changes in early congenital syphilis in 59 cases reveals that the changes of rarefaction zones and double contours are best explained on the basis of qualitative disturbances of growth.[70] The zones are not necessarily indicative of active syphilis but show the results of prior disease. A wide zone of normal bone epiphyseally indicates that the patient has been cured. Measurement of these zones makes possible an accurate determination of the onset of disturbance of bone growth. These changes are not the result of specific granulation tissue of destructive lesions. Generally, healing occurs without scar or deformity.

Reaction to Penicillin

A survey of the literature, analysis of published reports, a review of hospital records and a questionnaire to 15 selected clinicians were employed to determine the number of reactions to penicillin.[71] Despite the enormous increase in penicillin dosage the total number of reactions had remained low. An autopsy report of a death as a result of penicillin therapy in a case of gummatous aortitis has been reported in detail.[72] There was a marked inflammatory reaction that was interpreted as histologic evidence of a Jarisch–Herxheimer effect. An experimental reproduction of a local Jarisch–Herxheimer reaction by means of the introduction of immune serum suggested that the reaction is one of hypersensitivity.[73]

Natural Course of Syphilis

Although a great fund of knowledge has been accumulated in a constant search for the answers to many of the foregoing problems, several basic questions remain unanswered, and perhaps they will always be unanswerable. The natural course of the disease if left untreated has never been satisfactorily outlined. The well known survey of Bruusgaard is open to many criticisms. A more recent survey has been under way in Alabama for twenty years.[74] The original group was diagnosed as accurately as possible with the clinical and laboratory facilities available. At the same time a group of noninfected males of similar age and socioeconomic background were selected for purposes of comparison. At the end of twenty years the accuracy of the original diagnosis was confirmed by the treponema-immobilization test; of the 408 syphilitic patients, 165 were dead, and of the 192 nonsyphilitic subjects, 51 were dead. Sixty per cent of all these patients were autopsied. Life expectancy in the male Negro with untreated syphilis was reduced by 17 per cent, according to the study. This figure is considered to be valid and significant since the control subjects were basically from the same socioeconomic background as the syphilitic patients.

To ascertain the value of therapy in cardiovascular syphilis a survey of the world literature was made.[75] This was found to be of little value since there was no separation of the various types of cardiac involvement and no elimination of factors that might influence the outcome of either syphilitic or nonsyphilitic disease. Most important no controls were used since the seriousness of the disease would never justify the omission of therapy. An attempt to utilize a number of patients treated with older conventional methods as a control group also failed because a large enough series of similar cases could not be developed from the several large institutions participating.

Finally, a group of 1020 cases of syphilitic aortic insufficiency was studied retrospectively. These were selected from the files of two institutions and showed 30 per cent and 20 per cent survival rates after fifteen years. Of patients who were dead 75 per cent had a predominantly cardiac death. The autopsy studies showed an accuracy of diagnosis in 93 per cent in one hospital and 85 per cent in the other. The prognosis seemed to be better if the patient at the time of initial diagnosis was asymptomatic, not in failure or without angina. The effect of therapy could not be investigated from the data available.

In a survey of post-mortem material some interesting findings were disclosed.[76] During an eight-year period there were a total of 3104 neuropathological examinations in 14,311 general autopsies. Syphilis was thought to be present in 346 of these on the basis of the serologic tests and autopsy findings. In a group of 105 patients the diagnosis was established on neuropathological grounds, and in 72 per cent of these it was thought that syphilis could have been responsible for the symptoms described in the clinical records. In 126 cases there were post-mortem changes only of cardiovascular syphilis, and in this group 71 patients could have had their central-nervous-system symptoms on the basis of the cardiovascular disease. A total of 108 patients had symptoms of central-nervous-system involvement but no evidence of either cardiovascular or central-nervous-system disease at autopsy; all had positive serologic tests, and it is obvious that one should be cautious in evaluating symptoms with only a positive serologic test as confirmatory evidence. The risk of accepting syphilis as the cause of the presenting symptoms and not evaluating the entire picture with diagnostic studies is always present. Patients can have latent syphilis and also unrelated but treatable diseases of the cardiovascular and central nervous systems.

Since the late manifestations of syphilis develop a number of years after the initial infection the essence of venereal-disease control is the prevention of these. Since lack of therapy had been shown to be deleterious in its effect on life span a study was undertaken to determine why the disease progressed.[77] The venereal-disease program consists of three separate operations: case finding, case holding and treatment. After a thorough study of 687 patients with late syphilis, particularly of the central nervous system, it was found that opportunity for detection of late involvement was missed by physicians and hospitals in 38.4 per cent. Furthermore, of the same group 63.6 per cent were considered case-holding failures in that the patients did not receive adequate minimum treatment or were not adequately observed after treatment. The responsibility for these failures rests with the patient, physician and public-health program. With the frequent population shifts the prevention of disastrous late syphilis becomes not only a local but also a national problem.

The foregoing analyses of clinical findings and autopsy reports confirm the impression that syphilis in some manner reduces the expected longevity of each person infected. A worthwhile study was carried

out to see if this could be proved in laboratory animals.[78] A controlled experiment has shown that syphilitic mice had a marked reduction in life span as compared with the noninfected litter mates. The reason for this reduction is not known, but the hypothesis is advanced that it results from either a lowered resistance to all diseases or a general depression of the body defenses.

Much remains to be done in the future since several basic problems are still unsolved. These include "the successful growth of virulent *Treponema pallidum* on artificial media, the nature of immunity, the basis of tissue selectivity of the organism in man, the development of a practical and genuinely specific diagnostic test."[79]

Summary and Conclusions

Notable advantages of penicillin therapy still demand attention. This drug has shown its worth in all phases of syphilis. The results of long-term studies in the treatment of symptomatic neurosyphilis continue to be favorable. Another two decades will be required to establish the final value of this agent, but the promise continues to be bright. Other antibiotics are effective and can be utilized in persons who are allergic to penicillin. Local use of cortisone in interstitial keratitis warrants further study before the merits of this totally different method of management are determined. Certainly, in the early inflammatory phase, cortisone offers a great deal in control of the symptomatology.

The specificity of the treponema-immobilization test has become an established fact. The problems in making this test readily available are tremendous. Its place in differentiating false-positive reactions will stimulate further studies in this regard. Perhaps some of the immunologic factors in syphilis will be revealed through the use of the procedure.

Control and eradication of syphilis both in the nation and throughout the world are still far away. The optimistic belief that penicillin would erase syphilis has been dispelled. Certainly, the incidence of syphilis has experienced a sharp drop, but this only calls for increased efforts. The precise knowledge of the adverse effects of syphilis on longevity now available impels one to prevent the development of late syphilis. The treatment is available and is effective in at least 90 per cent of patients with early syphilis. Case-finding and case-holding activities must be the duties of all who undertake the responsibility of managing a single syphilitic patient.

References

37. Curtis, A. C., et al. Penicillin treatment of syphilis. *J.A.M.A.* **145**:1223-1226, 1951.
38. Thomas, E. W., Rein, C. R., Landy, S. E., and Kitchen, D. K. Results of treatment of early syphilis with single injection of procaine penicillin in oil and aluminum monostearate. *Am. J. Syph., Gonor. & Ven. Dis.* **37**:374-376, 1953.
39. Smith, C. A., O'Brien, J. F., Simpson, W. G., Harb, F. W., and Shafer, J. K. Treatment of early infectious syphilis with N, N' dibenzylethylenediamine dipenicillin G. *Am. J. Syph., Gonor. & Ven. Dis.* **38**:136-142, 1954.
40. Thomas, E. W., and Landy, S. Report on 726 patients who were re-treated following penicillin therapy for early syphilis. *Am. J. Syph., Gonor. & Ven. Dis.* **34**:126-143, 1950.
41. Schoch, A. G. Fallacious failure rates in treatment of early syphilis. *Arch. Dermat. & Syph.* **65**:714-722, 1952.
42. Rose, A. S., and Carmen, L. R. Clinical follow-up studies on 130 cases of long-standing paretic neurosyphilis treated with penicillin. *Am. J. Syph., Gonor. & Ven. Dis.* **35**:278-283, 1951.
43. Perlo, V. P., Rose, A. S., Carmen, L. R., and Soloman, H. C. Treatment of neurosyphilis — one- to six-year follow-up of patients treated with penicillin at the Boston Psychopathic Hospital — comparison of results with penicillin alone and combined penicillin-malaria therapy. *Am. J. Syph., Gonor. & Ven. Dis.* **35**: 559-567, 1951.
44. Hahn, R. D. Treatment of neurosyphilis with penicillin and with penicillin plus malaria. *Am. J. Syph., Gonor. & Ven. Dis.* **35**: 433-470, 1951.
45. Curtis, A. C., Kruse, W. T., and Norton, D. H. Neurosyphilis. IV. Posttreatment evaluation four to five years following penicillin and penicillin plus malaria. *Am. J. Syph., Gonor. & Ven. Dis.* **34**:554-565, 1950.
46. Ingraham, N. R., Jr., Stokes, J. H., and Gammon, G. D. Penicillin alone in neurosyphilis: spinal fluid response including a comparison with prepenicillin therapy. *Am. J. Syph., Gonor. & Ven. Dis.* **34**:566-580, 1950.
47. Dattner, B. Follow-up report on penicillin failures in neurosyphilis. *Am. J. Syph., Gonor. & Ven. Dis.* **34**:373-377, 1950.
48. Ford, W. T., Wiggal, R. H., and Stokes, J. H. Penicillin therapy of asymptomatic neurosyphilis: spinal fluid cell count as guide to therapeutic responses and re-treatment. *Arch. Int. Med.* **88**:235-242, 1951.
49. Thomas, E. W. Blood and spinal fluid tests for reagin after treatment of neurosyphilis. *J.A.M.A.* **153**:718-722, 1953.
50. Gammon, G. D., Lewey, F. H., Dillon, H., Schwarz, G., and Stokes, J. H. Pathologic observation of penicillin-treated neurosyphilis. *Am. J. Syph., Gonor. & Ven. Dis.* **34**:227-235, 1950.
51. Kenney, J. A., and Curtis, A. C. Treatment of syphilitic optic atrophy by penicillin, with and without therapeutic malaria. *Am. J. Syph., Gonor. & Ven. Dis.* **37**:449-457, 1953.
52. Benton, C. D., and Harris, J. F. Syphilitic optic nerve atrophy treated with penicillin: observations 2 to 6 years after treatment. *Arch. Ophth.* **48**:449-454, 1952.
53. Stokes, J. H., Wolferth, C. C., Edeiken, J., Falk, M. S., and Ford, W. T. Treatment of cardiovascular syphilis. *J.A.M.A.* **147**: 944-949, 1951.
54. Eisenberg, H., and Brandfonbrener, M. Observations on penicillin-treated cardiovascular syphilis. I. Uncomplicated aortitis. *Am. J. Syph., Gonor. & Ven. Dis.* **37**:439-441, 1953.
55. *Idem.* Observations on penicillin treatment of cardiovascular syphilis. II. Complicated aortitis. *Am. J. Syph., Gonor. & Ven. Dis.* **37**:442-448, 1953.
56. Wheeler, C. E., and Curtis, A. C. Treatment of cardiovascular syphilis with penicillin. *Am. J. Syph., Gonor. & Ven. Dis.* **35**: 319-328, 1951.
57. Barnett, C. W., and Small, A. A. Effect of treatment on prognosis of cardiovascular syphilis. *Am. J. Syph., Gonor. & Ven. Dis.* **34**: 301-318, 1950.
58. Klauder, J. V. Blindness due to syphilis. *J. Ven. Dis. Inform.* **32**:183-192, 1951.
59. Klauder, J. V., and Meyer, G. P. Early diagnosis of syphilitic primary optic nerve atrophy. *Arch. Ophth.* **43**:537-552, 1950.
60. Freeble, C. R., and Donohue, J. F. Syphilis and gonorrhea as causes of blindness. *J.A.M.A.* **146**:1500-1506, 1951.
61. Klauder, J. V., Gross, B. A., and Hanno, H. A. Endocrine studies of patients with syphilitic interstitial keratitis. *Am. J. Syph., Gonor. & Ven. Dis.* **35**:416-432, 1951.
62. Crane, G. W., Jr., and McPherson, S. D., Jr. Effect of local cortisone in treatment of syphilitic interstitial keratitis. *Am. J. Syph., Gonor. & Ven. Dis.* **35**:525-531, 1951.
63. Woods, A. C. Cortisone in interstitial keratitis. *Am. J. Syph., Gonor. & Ven. Dis.* **35**:517-524, 1951.
64. Shaffer, L. W., and Courville, C. J. Effectiveness of penicillin in prevention of congenital syphilis with note on effect of cowpox vaccination on serologic tests of seronegative infants. *Am. J. Syph., Gonor. & Ven. Dis.* **36**:457-467, 1952.
65. Nelson, N. A., and Struve, V. R. Prevention of congenital syphilis. *Am. J. Syph., Gonor. & Ven. Dis.* **36**:346-352, 1952.
66. Rein, C. R., and Kostant, G. H. Special diagnostic and therapeutic problems in syphilis. *Am. J. Syph., Gonor. & Ven. Dis.* **36**:301-308, 1952.
67. Avon, H. C. S., Parkhurst, G. E., Rodriquez, J., and Harris, W. W. Further observations on biologic false positive serologic tests in young children. *Am. J. Syph., Gonor. & Ven. Dis.* **36**: 278-283, 1952.
68. Thomas, E. W., de Mello, L., and Landy, S. Seroresistance following treatment of secondary syphilis. *Am. J. Syph., Gonor. & Ven. Dis.* **36**:319-331, 1952.
69. Peabody, G. E., Reader, G. G., Dotter, C. T., Steinburg, I., and Webster, B. Angiocardiography in diagnosis of cardiovascular syphilis. *Am. J. M. Sc.* **219**:242-248, 1950.
70. Engeset, A., Eek, S., and Gilje, O. On significance of growth in roentgenological skeletal changes in early congenital syphilis. *Am. J. Roentgenol.* **69**:542-556, 1953.
71. Kitchen, D. K., Rein, C. R., Thomas, E. W., and Spoar, H. J. Reactions to penicillin. *Am. J. Syph., Gonor. & Ven. Dis.* **35**: 578-582, 1951.
72. Whorton, C. M., and Denham, S. W. Occurrence of Jarisch–Herxheimer reaction in patient with gummatous syphilitic aortitis. *Am. J. Syph., Gonor. & Ven. Dis.* **35**:255-262, 1951.
73. Sheldon, W. H., Heyman, A., and Evans, L. D. Production of Herxheimer reactions by injection of immune serum in rabbits with experimental syphilis. *Am. J. Syph., Gonor. & Ven. Dis.* **35**:405-410, 1951.
74. Shafer, J. K., Usilton, L. J., and Gleason, G. A. Untreated syphilis in male negro. *Pub. Health Rep.* **69**:684-690, 1954.
75. Webster, B., et al. Studies in cardiovascular syphilis. III. Natural history of syphilitic aortic insufficiency. *Am. J. Syph., Gonor. & Ven. Dis.* **37**:301-329, 1953.

76. Wilson, G., et al. Substratum of central nervous system manifestations in syphilis. *Am. J. M. Sc.* **220**:84-86, 1950.
77. Thomas, E. W., Shafer, J. K., Zwally, M. R., and Price, E. V. Factors leading to development of late manifestations of syphilis. *Am. J. Syph., Gonor. & Ven. Dis.* **38**:531-553, 1954.
78. Rosahn, P. D. Adverse influence of syphilitic infection on longevity of mice and men. *Arch. Dermat. & Syph.* **66**:547-568, 1952.
79. Moore, J. E. Passing of *American Journal of Syphilis. Am. J. Syph., Gonor. & Ven. Dis.* **38**:487, 1954.

MEDICAL INTELLIGENCE

DOCTORS AFIELD

Francis Brett Young

JOHN LISTER, M.D.

LONDON, ENGLAND

FRANCIS Brett Young had a wide reading public on both sides of the Atlantic and will be remembered as a popular and prolific writer, rather than as a practicing physician. Nevertheless, he had a strong medical tradition behind him and was actively engaged in practice for a number of years. He was born in 1884 into a medical household. His mother came from a Midland medical family, and his father was a general practitioner at Halesowen in Worcestershire. This became the "Halesby" of his novels and was only a few miles from his "North Bromwich," which was Birmingham.

As a medical student in Birmingham his friends remember him as a young man who had a strong urge toward artistic creation of all kinds. He loved poetry and music and, above all, had a passion for his native Worcestershire. Indeed, it was Worcestershire that formed the heart of the region he was to make his own as a novelist — a region that stretched from the coalfields of the Black Country to the green borderlands of the Severn Valley and whose contrasts provided inspiration and imagination for his work.

Musical festivals, literary meetings and country rides and walks were his youthful recreations. For all that came from Worcestershire he had a special love. Because of this the musical work of Elgar was among his favorites, and he recalled hearing the first performance of the "Dream of Gerontius" in Worcester Cathedral. Again, the Worcestershire poet, A. E. Housman, gave him inspiration for setting poetry to music, and his setting of Housman's *Shropshire Lad* was often sung in student gatherings.

Shortly after graduating he married and in 1908 settled in general practice in the South Devon coastal town of Brixham. He deliberately chose a not too busy practice, for he hoped to devote as much time to writing as possible. His first novel *Undergrowth,* which appeared in 1913, was written in collaboration with a young brother. The book showed unmistakable promise and was followed in the next year by *Deep Sea,* which had Brixham for its setting.

Except for an interval spent as a ship's surgeon on a voyage to Japan, he remained in general practice until the outbreak of World War I. In 1915 he joined the Royal Army Medical Corps and was posted to East Africa, where he served under General Smuts as medical officer to a Rhodesian regiment. While in Rhodesia and South Africa he made friendships that led to subsequent visits and provided material for future writing.

After leaving the Army in 1918 he abandoned medicine for writing, and, instead of returning to his practice, he went to live in Capri. There, he was in company with other men of letters, such as Compton Mackenzie, D. H. Lawrence and Axel Munthe, and during the next ten years he produced a dozen successful novels. In these Young's medical training and experience are clearly discernible. He continually drew on his years of work as a general practitioner for the substance of his fiction. Indeed, his novels almost always derive in setting from a chapter of autobiography. Medicine, Birmingham, East Africa and, most of all, the familiar landscape of childhood are all phases of personal experience that he directs to imaginative ends.

The Birmingham Medical School formed the background for *The Young Physician,* and *My Brother Jonathan* and *Dr. Bradley Remembers* combined memories of parental practice with experiences of his own. His impressions of the East African campaign are vividly reflected in *Marching on Tanga;* he also wrote a slender book of verse about Africa, *Five Degrees South.* It was *Portrait of Clare,* however, that ensured his success as an author. This novel, which appeared in 1927, portrayed an unremarkable product of Worcestershire Society. It was awarded the James Tait Black Memorial prize. Many of his later novels also portrayed the English scene, but in 1937 a South African novel, *They Seek a Country,* appeared, and, two years later, *The City of Gold,* which was a graphic study of South African events from the founding of Kimberley to the Jameson raid.

During the years between the wars he made frequent visits to England and bought a charming eighteenth-century house in Worcestershire. He spent each summer there, returning to Capri to winter. While in England he played a part in the life of his county and took an interest in cricket and fruit farming. He remained in England throughout World War II, but he was too old for active service, and during those years he wrote the series of forty-six poems illustrating the history of England and published in 1944 under the

title of "The Island." This is a cavalcade of English history rendered in lyric, ballad, elegy, narrative and dialogue. It bears the stamp of all that was English in Francis Brett Young and stemmed from his deep interest in the history of England and in his love of the English countryside and its folk. This was his last great work, for, immediately after the war, he retired to South Africa, where he spent the last nine years of his life.

One of his greatest pleasures came when he made a brief visit to England and his old University conferred on him the honorary degree of D.Litt. Not only was this a personal honor but also it was an honor for the Birmingham medical faculty, because it has been said that he was the first Birmingham medical graduate to rise to such eminence in the Arts.

He died early in 1954 in Cape Town at the age of seventy.

CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 41091

PRESENTATION OF CASE

First admission. A fifty-nine-year-old banker was admitted to the hospital because of hypertension and renal calculi.

For fifteen years he had been passing small renal calculi periodically without pain, the most recent one having been passed a week before admission. He had had only one episode of dysuria, without chills or fever. Seven or eight years before admission he was told that his blood pressure was 180 systolic, and one year before admission it was 210 systolic. He was asymptomatic until six months before admission, when mild, diffuse headaches that were easily relieved by aspirin developed. He also had mild palpitations and dyspnea without orthopnea or ankle edema.

The past history revealed that he had been well, with no operations.

Physical examination disclosed a well developed, well nourished man. The fundi showed hemorrhages and exudates with spastic arterioles. The neck veins were flat. There was slight emphysema; both leaves of the diaphragm were low. The apex of the heart was at the fifth left intercostal space, 12 cm. from the midsternal line. The heart sounds were forceful, and the aortic second sound was slightly louder than the pulmonic. Dorsalis-pedis pulses were not palpable, but there were bilateral forceful posterior-tibial pulses.

The temperature was 98°F., the pulse 90, and the respirations 21. The blood pressure was 250 systolic, 160 diastolic.

Urinalysis was negative except for 8 red blood cells per high-power field in the sediment. Examination of the blood showed a red-cell count of 4,160,000 and a white-cell count of 14,000, with a normal differential. The blood Hinton test was negative. The calcium was 8.5 mg., the phosphorus 3.7 mg., the alkaline phosphatase 2.7 mg., the uric acid 5.9 mg., the cholesterol 164 mg., the nonprotein nitrogen 21 mg., and the fasting blood sugar 100 mg. per 100 cc. A stool was guaiac negative. An electrocardiogram suggested hypertrophy of the left ventricle, with P waves suggesting mitral-valve disease or considerable hypertension. The basal metabolic rate was +6 per cent. An x-ray film of the chest revealed a prominent left ventricle and a tortuous and elongated aorta (Fig. 1). An intravenous pyelogram showed fairly good concentration, with several small calcifications overlying the middle and upper portions of the left kidney. The floor of the bladder was consistently elevated, indicating prostatic enlargement.

The patient was discharged on the third day on a low-salt diet and phenobarbital.

Second admission (ten months later). Since discharge he had become worse. Suboccipital headaches and logginess developed, forcing him to give up work five months before admission. He would not stay on a low-salt diet but took phenobarbital regularly. Raudixin and Veriloid were tried without benefit.

Three months before admission a severe, searing pain suddenly appeared in the region of the right scapula, spread to upper lumbar regions in five to ten minutes and was associated with a substernal constriction. Nitroglycerin tablets promptly relieved the substernal discomfort, but the back pain continued for an hour and a half until it was relieved by sedation. The electrocardiogram then suggested coronary-artery disease and hypertrophy of the left ventricle. He was digitalized during the attack and maintained on digitalis. There were no neurologic signs or symptoms with the attack. He had noted inability to make a fist and to hold his toothbrush because of pain in the hand. The heart rate had risen from 80 to 100 two weeks before admission. There was no dysp-

nea. He had passed three or four small urinary stones since the previous admission.

Physical examination revealed no distended neck veins when he was lying in a position of 30°. There was early papilledema. There was a loud apical presystolic gallop and a Grade 2 left parasternal systolic murmur; the pulmonic second sound equaled the aortic. The liver edge was felt 2 fingerbreadths below the right costal margin. There was weakness of manual grip bilaterally.

The temperature was 98.2°F., the pulse 100, and respirations 20. The blood pressure was 270 systolic, 170 diastolic.

Urinalysis showed a ++ test for albumin and a specific gravity of 1.018; the sediment was loaded with red blood cells. Examination of the blood revealed a hemoglobin of 14.8 gm. per 100 cc., a white-cell count of 12,500, with a normal differential, and a sedimentation rate of 18 mm. in one hour. The nonprotein nitrogen was 22 mg., and the cholesterol 251 mg. per 100 cc. An electrocardiogram disclosed

FIGURE 1. *Posteroanterior Roentgenogram of the Chest Taken during the First Admission, Showing an Aorta Only Slightly Tortuous.*

more depression of the ST segments, with greater inversion of the T waves in Leads V_4, V_5 and V_6. An x-ray film of the chest revealed a tortuous thoracic aorta, with a definite suggestion that it was wider than on the previous examination (Fig. 2). Decreased amplitude of pulsation in the left ventricle was noted fluoroscopically.

Protoveratrine, 0.9 to 1.1 mg. four times a day was given, resulting in an undulating blood pressure and pulse rate with readings as low as 140 systolic, 90 diastolic, and as high as 240 systolic, 140 diastolic. The patient was discharged on the ninth day free of headache. Protoveratrine four times a day was prescribed.

Third admission (four months later). He was readmitted to the hospital because of an attack of acute pulmonary edema the night before, when he had a blood pressure of 260 systolic, 190 diastolic, a pulse of 130 and a pulsus alternans of 2 cm., with a +++ gallop. The protoveratrine had been discontinued for twenty-four hours because of nausea. Protoveratrine

FIGURE 2. *Posteroanterior Roentgenogram of the Chest Ten Months Later, Showing a Marked Increase in the Width of the Transverse and Descending Portions of the Thoracic Aorta.*

given intravenously reduced the blood pressure to 140 systolic, 80 diastolic, with associated nausea and vomiting.

On admission the blood pressure was 260 systolic, 170 diastolic, the pulse 100, and the respirations 22.

The nonprotein nitrogen was 27 mg. per 100 cc., and the chloride 97 milliequiv., and the sodium 136 milliequiv. per liter. An x-ray film of the chest showed a small amount of pleural fluid bilaterally, engorgement of pulmonary vascular shadows and no appreciable change in the configuration of the heart or aorta. The patient was placed on hexamethonium as well as protoveratrine and hydralazine and was discharged on this medication slightly improved on the fifteenth day.

Final admission (eight months later). He was admitted to the hospital because of increasing aphasia of seventy-two hours' duration and a seizure on the day of admission. Since discharge he had been switched to pentapyrrolidinium, 18 to 25 mg. four times a day by injection, and had returned to work part time. For two or three weeks he had experienced difficulty in remembering names. Two days

before admission aphasia developed and was worse during the next day. He became drowsy in the afternoon and had a convulsion involving all limbs, but was not incontinent and did not bite his tongue. He was confused and disoriented after the seizure and was brought to the hospital.

On physical examination the only new findings were the aphasia and Cheyne–Stokes respirations. Neurologic examination was negative except for + Hoffmann reflex on the left and slight weakness of the right arm and leg although he could walk. He was able to speak only an unintelligible jargon.

Laboratory data were unchanged since the last admission. An x-ray film of the chest showed improvement in pulmonary congestion.

Heparin and Dicumarol were given. A lumbar puncture on admission showed a protein of 76 mg. per 100 cc. and only 3 lymphocytes per cubic millimeter. On the third hospital day, a neurologic examination elicited weakness of the right extremities, an accentuation of the deep tendon reflexes on the right and aphasia. The Cheyne–Stokes breathing disappeared after a week in the hospital. The patient was discharged on the thirteenth day; the aphasia had improved strikingly, but he was still unable to add or multiply numbers on discharge.

Three weeks after discharge he awoke at 4 a.m. complaining of tingling in the right arm and leg and promptly became comatose. He had several generalized convulsions and died two hours later. In the interim the aphasia had disappeared, and his ability to calculate had improved strikingly.

Differential Diagnosis

Dr. Edwin O. Wheeler*: This appears to be a case of severe hypertension with a remarkable number of the sequelae and complications of hypertension. The patient had also been treated with a remarkable number of drugs, apparently not very effectively.

Dr. Benjamin Castleman: Here are the electrocardiograms.

Dr. Wheeler: The initial electrocardiogram when he first came to the hospital is consistent with hypertrophy of the left ventricle, for which there is increasing evidence on the next electrocardiogram.

Before discussing the various possibilities, I should like to see the x-ray films.

Dr. Joseph Hanelin: The pyelogram made at the first admission shows the kidneys to be normal in size; unfortunately, they are overshadowed by gas so it is a little difficult to see the calcifications although small densities can be made out overlying both kidneys. The kidneys function well and excrete the dye promptly.

Dr. Wheeler: Are the calcifications in the upper pole, or can you tell?

Dr. Hanelin: On the left side I think they are situated in the midportion of the kidney, probably lodged in the calyxes. The next series of films were made at the various admissions. In the initial film one can see the slightly prominent left ventricle and elongated aorta (Fig. 1). The lungs are emphysematous but are clear, and there is no definite congestion. Ten months later there is a striking change in the appearance of the aorta, which has become distinctly wider in its transverse and proximal descending portions, now showing a somewhat undulating contour (Fig. 2). The vessels appear slightly engorged, but there is no pleural fluid. The heart has increased somewhat in size. Four months later, there is evidence of congestive heart failure — engorged vessels, pulmonary edema and what appears to be a small amount of fluid at the base, particularly on the left side. The aorta has changed very little; perhaps it has become slightly wider but not appreciably so. Eight months later the lungs are clear of any congestive change. The heart and aorta have remained essentially the same in size and configuration.

Dr. Wheeler: There is a great amount of material to discuss in this case. In the first place, there is no particular reason to believe that the hypertension was anything but so-called essential hypertension. The patient had had renal stones off and on for many years, but aside from this he had no other striking evidence of renal disease. The red cells in the urine on the first admission may well have been related to the calculi. The nonprotein nitrogen and the intravenous pyelogram at that time suggest that he had no significant degree of renal disease so that it is unlikely that the hypertension was on the basis of a renal abnormality. The less common causes of hypertension are not suggested. I shall simply conclude that he had severe essential hypertension.

He had a number of the complications of hypertension. The common ones are renal, cardiac and cerebral involvement. There was not much evidence of renal involvement. During the second admission and presumably thereafter there was albuminuria and possibly red cells in the sediment. These may have been evidence of early renal disease; however, it is also possible that the red cells and perhaps the albumin were related to bleeding as the result of the stones. In any event the fact that nonprotein nitrogen remained normal up to the time of death suggests that he did not have serious renal disease.

Cardiac involvement, of course, was present from the first. At the time of the first admission, he had cardiac enlargement — hypertrophy of the left ventricle — as indicated by the x-ray examination of the chest and the electrocardiogram. However, there was no evidence of myocardial weakness or decompensation. Thereafter, the course, in part at least, was that of progressive hypertensive heart disease. At the time of the second admission there was evidence of increased cardiac hypertrophy, a presystolic gallop and a pulmonic second sound that was apparently louder than at the time of the first admission, all of

*Assistant physician, Massachusetts General Hospital.

which suggest early weakness of the left ventricle. At the time of the third admission he actually had an episode of acute pulmonary edema with pulsus alternans, a loud gallop rhythm and x-ray evidence of pulmonary congestion, so that there is no doubt that hypertrophy of the left ventricle developed over the years as the result of the hypertension and led to congestive heart failure, although it was not the cause of death.

The history suggests another cardiac or cardiovascular complication — that is, the episode of pain seven months after the first admission. The pain was located principally in the right scapular region, with radiation to the upper lumbar regions. There was some substernal discomfort that was described in different terms, suggesting two different types of discomfort. The substernal discomfort was promptly relieved by nitroglycerin whereas the pain in the back and lumbar region was not. The location of the pain and its radiation strongly suggest dissecting aortic aneurysm. The radiation to the back is unusual in coronary pain, and certainly radiation to the upper lumbar region is most unusual. It is possible that at the time of the aortic dissection there was a temporary interference with coronary circulation, which was responsible for the substernal constriction. There is not much to suggest coronary thrombosis with or without myocardial infarction, although the electrocardiogram probably showed changes since the diagnosis of coronary-artery disease was entertained. It is also possible that the patient had coronary atherosclerosis since he was in his late fifties and hypertensive. Finally, the diagnosis of dissection of the aorta is confirmed by the changes that occurred in the aorta in the time between these two films (Fig. 1 and 2), the latter of which shows marked widening of the arch and descending portion of the thoracic aorta. Whether the distress in the right hand can be explained by a neurologic abnormality or a vascular abnormality resulting from the dissection I cannot say at present. This brings us up to the patient's final complication, a cerebral one.

The first cerebral episode that occurred twenty-one months after the first admission was characterized by a slow onset of aphasia over a period of two days; one convulsive episode, apparently a clonic convulsion; and later or at the same time evidence of mild hemiplegia on the right, with weakness of the right arm and right leg and increased deep tendon reflexes. In addition the cerebrospinal fluid probably had a normal pressure and did not show any red cells. I suspect that he had a cerebral thrombosis; the slow onset and the relatively normal spinal-fluid findings make this likely. With a cerebral hemorrhage, he probably would not have survived; the onset should have been sudden, and the spinal fluid bloody and under increased pressure. There was no source for a cerebral embolus. I shall conclude that he had a cerebral thrombosis at that time. The fact that he was given heparin and Dicumarol suggests that his physician likewise did not consider cerebral hemorrhage likely. He recovered from this cerebrovascular accident.

The final episode bothers me. There was very little information about it because he died so rapidly. He apparently awoke at 4 a.m., complaining of tingling in the right arm and leg, and then became comatose. He had several generalized convulsions and died two hours after the onset. The bothersome thing is the suddenness of the death. Patients with cerebral thrombosis and cerebral embolism usually do not die within a period of two hours. Even the majority of patients with cerebral hemorrhage live longer than that. Simply on the basis of the time interval of only two hours between the onset of the episode and death, I shall make a diagnosis of cerebral hemorrhage although in view of the previous cerebrovascular accident the temptation is to say that he had another cerebral thrombosis. In conclusion, then, I should make a diagnosis of severe essential hypertension, dissecting aneurysm of the aorta, which had healed, and death as a result of cerebral hemorrhage.

Dr. Paul D. White: I saw this patient, but Dr. Currens knows much more about him. I should like to call attention to the fact that we rarely get such conclusive evidence of change in the size of the aorta as we have here, because the majority of such patients die too soon or because they are not followed so well, and the films are not so satisfactory as they are in this case.

Dr. James H. Currens: This case illustrates the situation that we are seeing more frequently these days— that is, that the treatment of hypertension with drugs frequently results in subjective and objective improvement, but the patient eventually dies of a stroke, dissecting aneurysm or one of the many complications of hypertensive disease. This man was helped appreciably by medicines that he received during the last fourteen months of his life.

Protoveratrine helped the headaches, but after four months nausea and vomiting became a problem and he chose to discontinue the medicine. While he was taking protoveratrine there was good evidence of lowering of the blood pressure and pulse rate for five or six hours after each of three daily doses. Hexamethonium and pentapyrrolidinium were next tried, and both were effective for three or four hours after injection. However, the lack of salivation was quite severe with these medications and made it difficult for him to eat because of dryness of the mouth. This lack of salivation was even worse if he took either drug by mouth and was so bad that he refused to take either orally in spite of the fact that he obtained more sustained control of the blood pressure by this route. Pilocarpine in adequate dosage was of only transient benefit. Incidentally, we could not detect any significant difference in the duration of action of the two drugs by injection. Constipation was a

problem, but with adequate laxatives he was able to have a bowel movement every three or four days.

Hydralazine, which has been claimed to be helpful in conjunction with hexamethonium or pentapyrrolidinium, had no further beneficial effect on the blood pressure in dosages up to 1.0 gm. daily. The patient thought the drug resulted in some "indigestion." He was tried on the pure alkaloid from *Rauwolfia serpentina,* reserpine, but he refused to take this after a short time because of excessive stuffiness of the nose.

I should like to emphasize the unusual fluctuation of blood pressure that occurred in this patient, who was treated with ganglionic blocking agents by injection four times a day. In the morning, when he awoke, the blood pressure was frequently 270 systolic, 170 diastolic, and two hours later after arising and after injection of one of the two drugs the systolic pressure was often less than the diastolic was on awakening — that is, about 150 to 160 systolic, 100 to 120 diastolic. The blood pressure gradually increased in the next two hours.

During the first few months of therapy there was pain in the left upper portion of the back and shoulder that was thought to be related to the dissecting aneurysm, but this disappeared after six months of treatment. The stiffness involving both hands, which is mentioned in the protocol, was thought to be due to the "shoulder-hand" syndrome and cleared up after about three months. The patient was able to return to part-time work for a period of a year with the help of these medications.

DR. WHITE: May I ask Dr. Colby whether he has encountered cases with renal calculi in which surgical correction has helped the blood pressure at the same time?

DR. FLETCHER H. COLBY: I operated on a girl yesterday who was hypertensive and had had a Smithwick procedure four years previously. She had had a stone in the left kidney for five years. Finally, because of persistent infection that did not clear up on antibiotics, I removed the stone. We did not believe that the stone had anything to do with the hypertension.

CLINICAL DIAGNOSES

Cerebrovascular accident.
Hypertension.
Healed dissecting aneurysm of aorta.

DR. EDWIN O. WHEELER'S DIAGNOSES

Cerebral hemorrhage, recent.
Cerebral thrombosis, old.
Essential hypertension.
Healed dissecting aneurysm of aorta.

ANATOMICAL DIAGNOSES

(Essential hypertension.)
Pontine hemorrhage, recent, massive.
Healed dissecting aneurysm of aorta (one and a half years).
Cerebral hemorrhage, old, left posterior temporal region.
Cardiac hypertrophy, hypertensive type.
Coronary sclerosis, moderate.
Nephrosclerosis.
Chronic pyelonephritis and nephrolithiasis, mild.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: This patient had a very large heart, weighing over 600 gm., with the characteristic hypertrophy associated with hypertension. He died, as Dr. Wheeler predicted, of a cerebral hemorrhage. Perhaps Dr. Richardson will describe that.

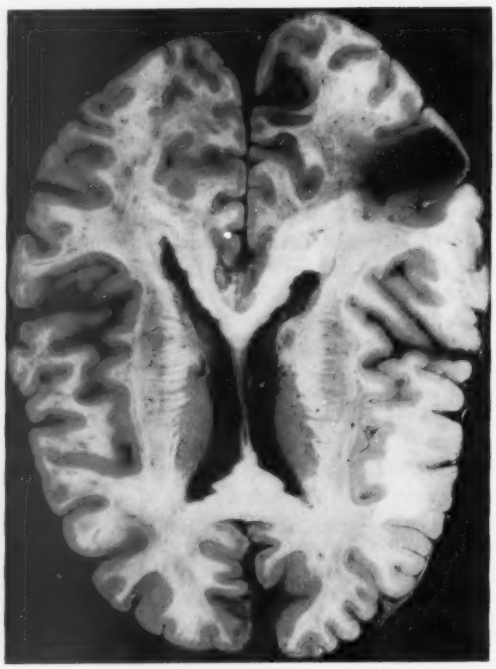


FIGURE 3.

DR. EDWARD P. RICHARDSON, JR.: In the first place there was a small hemorrhage 2 cm. or so in diameter in the left posterior temporal region (Fig. 3). This lesion was obviously old because of brownish discoloration of the blood, with a layer of organization around the edge. This was surely the cause of the aphasia that occurred some time before death. The location of the lesion is of some interest from the standpoint of clinical localization in view of the speech disorder. A small cerebral hemorrhage is unusual in our experience; when it is not due to an obvious vascular malformation, it has been seen in cases of severe hypertension. The cause of death was a pontine hemorrhage (Fig. 4). When cerebrovascular lesions

have caused death within an hour or two of their onset, they have invariably been brain-stem hemorrhages.

DR. CASTLEMAN: This patient had a healed dissecting aneurysm — one of the few that we have seen here. There was no dissection of the ascending aorta; perhaps that is the reason, Dr. White, that the patient lived after the dissection. Most patients have intimal tears in the ascending portion, and since the pressure is greatest in that location, death often results from external rupture at the same level.

DR. WHITE: You have, however, seen other patients with dissecting aneurysms who have lived?

DR. CASTLEMAN: Yes; but those cases are rare. We have had about 4 or 5 here.

The ascending aorta was normal. In the descending portion we found six large intimal openings — which were not openings of aortic branches (Fig. 5). The uppermost, just below the arch, was a healed horizontal slit, which I believe was the initial intimal tear; the blood then dissected down into the wall of

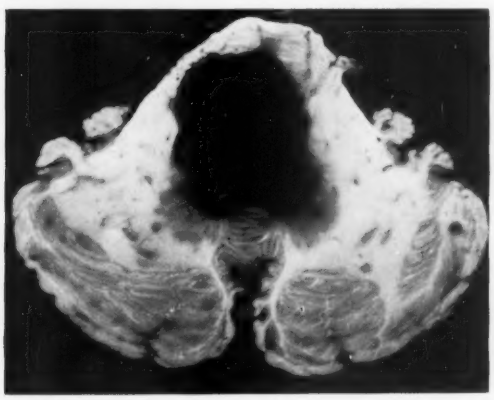


FIGURE 4.

the aorta and probably re-entered the original aortic lumen through the lowermost opening, located at the bifurcation. Between these entrance and exit openings were four other rounded openings that I am almost certain were secondary to the long-standing hematoma in the wall that apparently produced enough pressure on the intima to rupture back into it. At first we were not sure what these holes meant but careful sectioning of the aorta showed that they were all connected. The media was separated by the hematoma, which at this stage was replaced by organized connective tissue (Fig. 6).

DR. WHITE: Was blood still circulating in the dissection channel?

DR. CASTLEMAN: No. Blood entered some of the holes but was stopped by the organized hematoma.

DR. WHITE: Sometimes, there may be a small rupture in the aortic wall without much dissection, may there not?

DR. CASTLEMAN: In our experience that occurs only with severe arteriosclerosis, in which the break is on the basis of an atheromatous plaque with erosion; then there is a short dissection, but, so far as I know, it does not produce symptoms. The usual aortic dissection that produces symptoms is due to medial

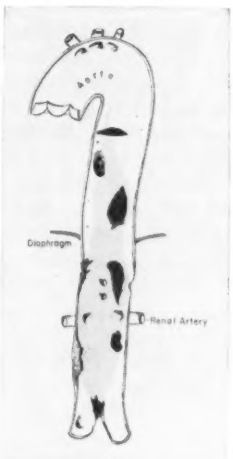


FIGURE 5. *Schematic Drawing of the Aorta, Showing Six Intimal Openings (Black).*
The shaded area represents the extent of the healed dissection channel.

disease not to arteriosclerosis. The arteriosclerosis seen in the case under discussion was secondary.

FIGURE 6. *Section through the Wall of the Aorta, Showing Disruption of the Elastic-Tissue Layer.*
A=*intima.* B=*organized hematoma in the media.* C=*fresh blood from intimal openings prevented from dissecting by the hematoma* (B).

DR. CURRENS: Was any necrotizing arteriolitis found at autopsy?

DR. CASTLEMAN: No; the kidneys contained a few stones and showed a very mild degree of pyelone-

phritis and moderate vascular change, which we should probably regard as Grade 2.

DR. WHITE: How were the coronary arteries?

DR. CASTLEMAN: All the coronary arteries were moderately sclerotic but were not occluded anywhere. There was no dissection around the coronary mouths.

DR. CURRENS: At the time drug treatment was initiated the patient had headache, papilledema, hemorrhages and exudates in the eyes, which suggest that at that time he had early necrotizing arteriolitis. This is what some physicians choose to call "malignant hypertension," which is a poor term because the criteria for its diagnosis are different for each physician who uses the term.

DR. CASTLEMAN: We found no evidence of it in either kidney.

DR. WHITE: The treatment may have helped to prevent that.

DR. CURRENS: Yes; it seems as though many patients can get along reasonably well with intermittent severe hypertension, in contrast to sustained severe hypertension.

CASE 41092

PRESENTATION OF CASE

A forty-seven-year-old man entered the hospital because of dyspnea, abdominal swelling and weakness.

For the previous three years he had felt run down, with some weight loss, and had had frequent colds without specific symptoms. During this period he was not well enough to be steadily employed and had worked only occasionally. About four months before admission he began to have pain in the right upper quadrant of the abdomen, a sensation of bloating and shortness of breath. There had also been frequent nausea, occasional anorexia, but no vomiting. He remarked that he had noticed a protuberance of the umbilicus over the past few months and had also become aware of enlarged hemorrhoids during this interval. One week previously he was admitted to another hospital, where he was treated with injections, which produced a diuresis, a subsidence of the abdominal swelling and a relief of dyspnea.

He admitted to a large alcoholic intake over a twenty-six-year period ending three years before admission. During most of this time, while he worked as a club steward, he began drinking in the latter part of the morning and continued for the remainder of the day. However, his statement that he had almost completely stopped the intake of alcohol for the past three years was confirmed by members of his family. Despite occasional anorexia he claimed to have eaten well over this three-year period until the previous few months.

There was no history of serious illness or operations. He recalled two episodes of pneumonia nine years and three years before admission. There had been frequent colds, especially during the previous three years, and a slightly productive morning cough. There was no history of hematemesis, melena, jaundice, light stools or dark urine. He denied ankle edema.

The temperature was 99.4°F., the pulse 88, and the respirations 20. The blood pressure was 120 systolic, 80 diastolic.

Physical examination showed a well developed, well nourished man. There was acne rosacea of the face. No jaundice or spider angiomas were observed. An unsustained nystagmus on extreme left lateral gaze was present. The tongue was smooth and red. Examination of the thorax revealed clear lungs, a high right leaf of the diaphragm with limitation in its motion and a normal heart. The umbilicus was protuberant, and the liver edge was palpable 7 fingerbreadths below the right costal margin and was hard, smooth and slightly tender. A questionable fluid wave was noted in the abdomen. The spleen was enlarged and could be felt 2 fingerbreadths below the thorax. The external genitalia were normal; rectal examination disclosed tenderness, external hemorrhoids and a normal prostate. There was no peripheral edema.

Urinalysis revealed a specific gravity of 1.016, a ++ test for albumin, negative tests for sugar and bile and occasional red and white cells and many hyaline and a few granular casts per high-power field in the sediment. Examination of the blood showed a hemoglobin of 13.6 gm. per 100 cc. and a white-cell count of 13,500, with 85 per cent neutrophils. The blood Hinton test was negative. The nonprotein nitrogen was 35 mg., the bilirubin 0.3 mg., the total protein 6.7 gm., with an albumin-globulin ratio of 2.0, and the alkaline phosphatase 4.6 units per 100 cc. The prothrombin time was 60 per cent of normal; a Congo-red test showed 56 per cent retention in the serum, and cephalin flocculation was negative after twenty-four and forty-eight hours. X-ray examination of the chest with a barium swallow revealed a linear scar in the right-midlung field, emphysema with dorsal kyphosis and elevation of the right leaf of the diaphragm. No esophageal varices were seen. Enlargement of the liver and spleen was suggested by the grid film.

On the fourth hospital day, a needle-biopsy specimen of the liver revealed no diagnostic abnormality. An operation was performed on the eighth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. JOHN A. BENSON, JR.*: I should like to review the available films and to ask Dr. Gibbons whether there was any hilar adenopathy, calcified lymph nodes in the mesentery, or sufficient gas and barium in the stomach to outline either varices or tumor.

*Assistant in medicine, Massachusetts General Hospital.

DR. JOHN F. GIBBONS: The only films that we have are those of the chest. We do not have any abdominal films. On the chest films, the linear atelectatic scar, which may be the result of old pneumonia, is seen in the right lung; the left leaf of the diaphragm is higher than it should be. The heart is not enlarged, and there are no varices in the barium-filled esophagus. I do not see any enlarged lymph nodes in the chest. On the grid film the stomach appears indented, probably by the enlarged liver; I think we can see the medial edge of the enlarged spleen. There are no calcified lymph nodes.

DR. BENSON: Is there any evidence of pulmonary tuberculosis?

DR. GIBBONS: No; there is not.

DR. BENSON: The punch biopsy of the liver is somewhat disconcerting, for, under usual circumstances, a diagnosis of cirrhosis might have been expected despite the liver-function tests; however, no diagnosis was forthcoming. I am assuming that sufficient lobular tissue was available for a satisfactory study and that congestion of the sinusoids with blood, occlusion or displacement of central veins and fatty infiltration were specifically absent. A negative biopsy should not be interpreted dogmatically, however, since isolated lesions can easily be missed. Even cirrhosis has been missed on repeated biopsies, although very rarely; so this condition, which most commonly accounts for the situation met in this case, has not been excluded. In the extensive experience of Ward et al.[1] a fifth of the patients with technically adequate biopsies that had failed to demonstrate neoplastic disease later proved to have it at laparotomy or autopsy. Ward and his associates report but 1 case of neoplasm missed by each of two biopsies. Therefore, repeated biopsies are indicated.

The ascites also merits a few general remarks. In the absence of cirrhosis two other causes of ascites may be considered. Portal hypertension, possibly manifested in this case by the splenomegaly and hemorrhoids, can be caused by thrombosis in the portal system or obstruction due to extrinsic pressure from enlarged lymph nodes or tumor. However, extrahepatic portal-bed block is not often associated with ascites in the absence of a low serum albumin and does not explain the enlarged liver. The biopsy failed to demonstrate the congestion associated with obstruction of the hepatic veins. The other mechanism for the production of ascites is peritoneal irritation caused by tuberculous peritonitis or carcinomatosis.

Reluctantly, I discard cirrhosis. The combination of negative liver-function tests and a negative biopsy obliges me to seek another disease.

I believe that the patient's illness falls into one of two categories — granuloma or malignant neoplasm.

Among the granulomas miliary tuberculosis with peritonitis seems an attractive diagnostic solution to this case. It could explain the findings on urinalysis, the chronic cough and the malaise since the pneumonia three years before admission. But, with most granulomas the liver, if enlarged at all, is only 2 or 3 fingerbreadths below the right costal margin, and in two thirds of the cases there is an elevated globulin. Furthermore, splenomegaly is uncommon except in sarcoidosis. There was no lymphadenopathy peripherally or in bronchial lymph nodes to support this diagnosis.

Malignant neoplasm is the other possibility. It seems unlikely that a cancer metastatic to the liver would not have declared itself in three years. But cancer of the stomach, body of the pancreas or lung certainly can remain silent and small and yet metastasize widely. Furthermore, tumor is almost always associated with hard hepatomegaly, and ascites can be produced by tumor nodules or involved lymph nodes obstructing the hepatic vasculature. I do not have sufficient evidence to make such a diagnosis, however. There was no elevation of the alkaline phosphatase, which exceeds 5 Bodansky units in 70 per cent of patients. Half such patients are jaundiced, and, incidentally, 90 per cent had bromsulfalein retention in the series of Ward and his co-workers.[1] For similar reasons, I tend to discount hepatoma. Primary liver cancer does occur without underlying cirrhosis in a third of the cases, but splenomegaly is usually not so conspicuous as in this case. It might be added that the smoothness of the liver should not deter one from considering neoplasm. Lastly, there was no jaundice or obstructive signs to suggest cholangioma.

A malignant condition that bridges the categories of neoplasm and granuloma — namely, Hodgkin's disease — seems to me to be the best possibility. The chronic course of symptoms, vague but sufficient to cause the patient to miss work, is appropriate. Liver involvement has been noted in about half the reported cases of Hodgkin's disease. Hepatomegaly may be extreme and may constitute the major objective finding. Ascites can be produced by compression on or infiltration of the portal vein and can be chyliform. The lesions may be miliary as well as nodular. Jaundice is uncommon and can be hemolytic as well as due to parenchymatous infiltration.

I have not overlooked the possibility of infection. The lack of significant pain, sweats, fever and chills led me to exclude cholangitis, pylephlebitis and abscess.

I propose that this man had Hodgkin's disease in the liver and in the abdominal lymph nodes, especially those at the porta hepatis. It was entirely proper to rebiopsy in this case to establish the diagnosis, and I assume that the second operation, which was done without the benefit of further x-ray examinations, was to obtain tissue, either by a second needle biopsy of the liver or by laparotomy or peritoneoscopy.

DR. ROBERT E. SCULLY: Dr. Ellis, should you like to comment?

DR. DANIEL S. ELLIS: Dr. Benson has given an ex-

cellent discussion. I believe that the only way one can reasonably explain this picture is on the basis of a malignant process. I find nothing in the protocol other than the history to suggest cirrhosis, and the laboratory data do not support that diagnosis. Dr. Benson assumed that the liver biopsy was a good specimen. Was it?

DR. SCULLY: Yes; it was adequate; it showed several lobules.

DR. ELLIS: This, in the face of the negative liver-function tests and large liver, favors neoplastic disease in the liver. Because the spleen was palpable I favor a lymphomatous type of malignant process rather than carcinoma even though every once in a while a spleen may be palpable with widespread metastatic carcinoma of the liver.

DR. JOHN G. FREYMANN: I should like to ask Dr. Benson which diagnosis would be easier to miss in a liver biopsy, Hodgkin's disease or a diffuse granuloma like sarcoidosis or miliary tuberculosis.

DR. BENSON: I cannot find any series large enough to give you a definite figure about the granulomas.

DR. ELLIS: I doubt if such a figure would be valid because often one does not know about the cases one misses. All the patients who have had biopsies have to come to autopsy to give a valid series of cases. Even at laparotomy metastatic carcinoma of the liver may be missed.

DR. EDWARD B. BENEDICT: It seems that in the past the negative needle biopsies of the liver have not been followed up too often by peritoneoscopy or laparotomy.

DR. ELLIS: I think they always are in patients who have large livers that are not explained. I think we would be negligent if we did not do a peritoneoscopy or laparotomy in these cases.

CLINICAL DIAGNOSIS

Malignant tumor of liver.

DR. JOHN A. BENSON, JR.'S, DIAGNOSIS

Hodgkin's disease of liver and abdominal lymph nodes.

ANATOMICAL DIAGNOSIS

Adenocarcinoma of liver, probably metastatic.

PATHOLOGICAL DISCUSSION

DR. SCULLY: The physicians who were taking care of this patient on the ward believed, as Dr. Benson and Dr. Ellis did, that the combination of hepatomegaly and negative needle biopsy indicated a malignant process. Dr. Benedict performed a peritoneoscopy and biopsy and perhaps will tell us what he saw.

DR. BENEDICT: I think Dr. Benson is quite right in emphasizing the point that negative biopsies do not mean much. I have been saying right along that a negative biopsy taken during any endoscopy does not rule out carcinoma or various other diseases. In this case the peritoneoscopy revealed a tongue of liver tissue in the right flank that was replaced by carcinoma.

DR. SCULLY: The second biopsy specimen showed an adenocarcinoma in which the tumor cells were forming small, duct-like structures. We believed, largely on the basis of statistical reasoning, that the tumor was a metastatic adenocarcinoma, although we were not able to rule out a primary cholangiocarcinoma. The absence of cirrhosis and the fact that the patient was a man are further evidence against the latter diagnosis. He was discharged without further studies since his family did not want to undergo unnecessary expense, and it was decided that nothing more could be done for him. Consequently, we may never establish the location of the primary tumor.

DR. WILLIAM H. BAKER: I should like to ask about the experience at this hospital regarding the incidence of primary liver carcinoma and cirrhosis. I did not realize that about a third of the patients with primary liver carcinoma have no cirrhosis.

DR. BENSON: That is the figure from recent experience.[2,3] I was surprised to read that too.

DR. SCULLY: Most statistics in the literature indicate that with hepatomas 80 to 90 per cent of the patients have an underlying cirrhosis, whereas with cholangiocarcinomas only about 50 per cent do. The cirrhosis is usually of a biliary type with the bile-duct carcinomas. I cannot give the exact figures for this hospital. However, it is my impression that we see primary carcinoma of the liver in the absence of cirrhosis less often than one would expect from the statistics in the literature.

REFERENCES

1. Ward, J., Schiff, L., Young, P., and Gall, E. A. Needle biopsy of liver. IX. Further experiences with malignant neoplasm. *Gastroenterology* **27**:300-306, 1954.
2. Galluzzi, N. J., Weingarten, W., Regan, F. D., and Doerner, A. A. Evaluation of hepatic tests and clinical findings in primary hepatic cancer. *J.A.M.A.* **152**:15, 1953.
3. Hauch, E. W., and Lichstein, J. Clinical problem of primary carcinoma of liver. *Gastroenterology* **27**:292-299, 1954.

The New England Journal of Medicine

Official Organ of
THE MASSACHUSETTS MEDICAL SOCIETY

OWNED BY THE SOCIETY AND
PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE
COMMITTEE ON PUBLICATIONS

Richard M. Smith, M.D., *Chairman*
James P. O'Hare, M.D. — Richard E. Alt, M.D.
Oliver Cope, M.D. — James M. Faulkner, M.D.

Joseph Garland, M.D., EDITOR

ASSOCIATE EDITORS
Thomas H. Lanman, M.D. — Donald Munro, M.D.
Theodore H. Ingalls, M.D.

Clara D. Davies, EXECUTIVE EDITOR
Robert O'Leary, ASSISTANT EDITOR
James F. Ballard, BOOK REVIEW EDITOR
Milton C. Paige, Jr., BUSINESS MANAGER

EDITORIAL BOARD
Henry R. Viets, M.D. — Benjamin Castleman, M.D.
Robert M. Green, M.D. — J. Englebert Dunphy, M.D.
Dwight O'Hara, M.D. — Robert W. Buck, M.D.
Fletcher H. Colby, M.D. — Herrman L. Blumgart, M.D.
Robert L. Goodale, M.D. — Frank N. Allan, M.D.
Chester M. Jones, M.D. — Harvey A. Kelly, M.D.
Harvey R. Morrison, M.D. — Langdon Parsons, M.D.
Maxwell Finland, M.D. — Mark Aisner, M.D.
Vernon P. Williams, M.D. — Walter F. Lever, M.D.

SUBSCRIPTION TERMS: $8.00 per year in advance, postage paid, for the United States (first-year interns and medical students, $5.00 per year); Canada, $9.00 per year (Boston funds); foreign, $10.50 per year. Long-term rates: United States, 2 years $15.00, 3 years $22.00; Canada, 2 years $17.00, 3 years $25.00; foreign, 2 years $20.00, 3 years $29.50.

MICROFILM volumes available to regular subscribers through University Microfilms, 313 N. First Street, Ann Arbor, Michigan.

MATERIAL, other than original articles, should be received not later than noon on Thursday, three weeks before date of publication.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

MANUSCRIPTS, including references or bibliography, should be typewritten double spaced and submitted as original copy. References should conform to the style of the *Quarterly Cumulative Index Medicus* (listing name and initials of author, title of article, journal, volume number, first and last pages and year), and should be cited numerically in the order in which they appear in the text; the number should be limited to the absolute minimum.

ILLUSTRATIONS are reproduced as half tones and zinc etchings. Photographs must be distinct, and drawings done in black ink on white paper and each properly labeled.

MATERIAL printed in the *New England Journal of Medicine* is covered by copyright. Articles are accepted for consideration with the understanding that they are contributed for publication solely in this journal.

CHELATING AGENTS

THE use of chelating agents to rid the body of undesirable metals is a discovery of considerable interest.[1-3] Chelating agents such as sodium ethylene diamine tetra-acetic acid, when administered to man or animals, have the property of incorporating metals into their molecules to render them un-ionized. This is demonstrated by the fact that these metals in vitro are not precipitated as their insoluble salts, but remain bound to the chelating agent. Thus, if one can administer such an agent and bind a toxic metal, the complex can be excreted through the kidney without the usual toxicity that follows chemical reactions of the metal with the body tissues.

The utilization of the calcium chelate of ethylene diamine tetra-acetic acid eliminates the development of low serum calcium tetany, which sometimes occurs with the sodium salt. The compound exchanges its calcium for a heavy metal for which it has a greater avidity, and excretes it un-ionized through the kidneys.

This technic is a distinct step forward in therapy, and it is obvious that this type of chemical action has a valuable function. Any drug that has such a marked pharmacologic effect can be expected to have toxic manifestations. Such evidence is presented in the paper by Dudley, Ritchie, Schilling and Baker in this issue of the *Journal*, and it indicates an area of the body that may be injured in association with the use of the sodium salt of EDTA. In both these cases large amounts of the sodium salt, approximately 200 mg. per kilogram of body weight, were administered continuously over a twenty-four-hour period for twelve and eleven days to control hypercalcemia. This report of toxicity should not eliminate the use of the drug for escorting heavy metals out of the body, as indicated by the success obtained in lead poisoning with a calcium salt.[4,5] Such a successful report is incorporated in the paper by Kneller, Uhl and Brem, also published herewith.

Since there are obvious dangers from the prolonged use of the sodium salt there may be undesirable effects of prolonged use of other salts. Recently, Kehoe[6] wisely objected to continued oral administration as a prophylaxis against lead poisoning. Cleanliness in manufacturing plants is safer than any drug — no matter how effective. Drugs with such potent therapeutic effects must have their limitations defined before they can be widely used with safety.

REFERENCES

1. Bessman, S. P., Reid, H., and Rubin, M. Treatment of lead encephalopathy with calcium versenate. *M. Ann. District of Columbia* **21**:312-315, 1952.
2. Belknap, E. L. EDTA in treatment of lead poisoning. *Indust. Med. & Surg.* **21**:305, 1952.
3. Foreman, H. *Use of Chelating Agents for Accelerating Excretion of Radioelements.* (University of California Radiological Laboratory 1694.) Berkeley, California: Atomic Energy Commission, February 28, 1952.
4. Hardy, H. L., Elkins, H. B., Ruotolo, B. P. W., Quinby, J., and Baker, W. H. Use of monocalcium disodium ethylene diamine tetra-acetate in lead poisoning. *J.A.M.A.* **154**:1171-1174, 1954.
5. Use of calcium ethylenediaminetetraacetate in treating heavy-metal poisoning. *Arch. Ind. Hyg. & Occup. Med.* **7**:137-147, 1953.
6. Kehoe, R. A. Misuse of edathamil calcium-disodium for prophylaxis of lead poisoning. *J.A.M.A.* **157**:341, 1955.

STURM UND DRANG

In his address at the Columbia University bicentennial J. Robert Oppenheimer is quoted as having said that the frontiers of science are separated now from the common heritage of even the most civilized society by specialized vocabularies and knowledge, that the scientist has neither a sense of community nor objective understanding in his relations with a wider society, that the modern artist is lonely because common experience has been dissolved in a changing world, and that men's lives are barren because they are deprived of an intelligible interpretation in contemporary terms of the sorrows and wonders of life.

The discouraged Dr. Oppenheimer is speaking only for himself. Actually, there was never a period in the world's history when so many were able to understand so much of what others were thinking as at present. Today more people have an understanding of the principles of atomic energy than were able to recite their ABCs in the Dark Ages. More men have a reasonable comprehension of both modern art and nuclear physics than were able to read at all in the days of Charles the Great.

Of course, artists are lonely — not only modern artists, but traditional ones. The literary scholar or cultivated gentleman of the nineteenth century finds no kindred soul today who perceives the delicate nuance of his Horatian quotations or appreciates his standards of propriety.

It need never be feared that one man will become so knowledgeable that none other will be able to outdistance him. In spite of the intellectual accomplishments of advanced thinkers in the fields of art or science, the fact remains that man's concepts are both created and limited by his five senses. Without them the whole structure of centimeter-gram-second knowledge would collapse. A dog, a bird or a bee, on the other hand, seems at times to have access to other channels of knowledge. Although scientists have been able to build bombs that will blast sizable areas of the earth's surface, they cannot construct a honeycomb, and even Picasso cannot produce anything so lovely as a damask rose.

VANISHING SEX

Under the prophetic title "The Coming Scarcity of Women," Ffrangcon Roberts, recently of Cambridge University, England, makes some interesting comments in the *Sunday Times* of November 21, 1954. The "intoxicating prediction" by the Chancellor of the Exchequer that Britain's standard of living can be doubled in the next twenty-five years, based on imminent revolutionary advances in technology, gets Dr. Roberts off to a running start. The Chancellor's prediction appears in some mysterious way to be supported by an expected increase of 500,000 souls in the working-age group.

Roberts reveals the fly in this particular ointment, however, by discussing a study of sex distribution in the working-age group; for Britain is plagued by an increasing excess of males in her increasing population. Thus, according to a projection of prevailing trends into the future, by 1983 the males in the working group will have increased by about 700,000 and the females will have decreased by nearly 500,000. By a simple arithmetical computation the present 500,000 excess of working males will be found to have increased by then to nearly 1,700,000.

This amazing shift in the British male-female ratio is occasioned in part by the recognized fact that everywhere the world around, but especially in Great Britain, more boys are born than girls, and partly by the reduction in infant and child mortality, which has worked to the benefit of the naturally more delicate boys. Whereas formerly the preponderance of males was lost by age ten, it now continues to age thirty, and by 1983 is expected to reach age fifty.

The complications that this disparity will produce, not only in industry but in the social and domestic life of the realm as well, can easily be imagined. Tasks now considered as peculiarly feminine will be taken over by men. In industry men will fill to an increasing degree positions as secretaries, stenographers and clerks, and the burden of household work will naturally fall to their share; even more so than at present.

The housing problem will be markedly affected, for, as Roberts points out, "Thousands of houses now occupied by families will have to be converted, not only into homes for the aged, but also into men's hostels, the inhabitants of which will have to fend for themselves." Primordial urges that are suspected of being stronger and certainly seem to be less disciplined in men than in women will struggle for expression even more fiercely than today, unless bigamy is perchance legalized. In the struggle for mates, as Roberts graphically expresses it, "Boys now in their cradles will crack one anothers' skulls like stags."

Failing a sex equalization through immigration from other, less "andrised" nations — a highly improbable solution — the gradual readjustment into a preponderantly male society will need to be made. Living in a thoroughly mechanized environment resulting from the expected continuing advances in technology, the dominant male will surround himself with all conceivable comforts — except those of home. Such a technocratic society will gain the entire world, but, as Roberts concludes, "without its ministering angels will it find life worth living?"

AMO, AMAS

As suggested by the reactions of the least amiable of Mr. Disney's seven dwarfs, the expression of love is often interpreted as a sign of weakness by those who like to be considered tough, regardless of manliness — superficially sophisticated regardless of cultural depth.

The uncultivated are inclined to treat the subject with puerile self-consciousness, and even those of greater emotional stability, if they discuss the matter at all, do so with reserve. And yet whereas many might fail to conjugate the emotion as a transitive verb, few would decline it as a noun.

Despite the aura of weakness, of softness, perhaps of silliness that seems to be inseparable from romantic love or infatuation as it is commonly viewed, one can scarcely deny that love in its broader aspects constitutes the main source of zoologic survival. It can also be a very complicated part of human existence, as Solomon points out in his special article on "Love: A Clinical Definition," published elsewhere in this issue of the *Journal.*

It must be admitted, so sensitive are human reactions, that the very use of the word in a medium devoted largely to realistic presentations may entail certain risks of misinterpretation, particularly from those who find that a snicker or a wisecrack is an easy way to bypass serious consideration. There seems, however, to be no way of avoiding the occasional use of the 4-letter word and at the same time retaining the ideas that it conveys.

Love, as Solomon points out, stems from the most basic affection of all — that for self — the indispensable factor in continued personal existence. Based on this concept, although the author does not mention it, even the ameba has its love life and could the ameba think, a certain agonizing reappraisal could be necessary each time cell division took place.

In the more complicated human being, love develops and progresses in what might be an orderly pattern but is more likely to be a confused one. Self-love finds security in mother love, then boy meets girl and infatuations develop. As Shakespeare so implacably demonstrated in the case of his child lovers of Verona, and Goethe, too, in *Die Leiden des jungen Werthers,* the course of true love (if that is what it is) does not run smoothly. It is at the level of romantic love carried to the point of infatuation that all the world loves a lover, even if public displays of affection are occasionally greeted with rude sounds.

The part that sex plays in love depends on one's definition of love and one's experience with it. Physical sex gratification seems to represent the highest level to which some persons' love can reach; the same can be said of goats. Others ascend higher peaks in Darien and enjoy somewhat loftier emotions, depending on their ability to give as well as to receive. As Solomon phrases it, "Even in mature love, the partners share in giving love to one another and to their life work as though they were giving to their eventual idealized selves."

CATASTROPHES OF 1954

CATASTROPHES, defined by Webster as sudden calamities or great misfortunes, are more precisely interpreted by the Information Service of the Metropolitan Life Insurance Company as accidents in which five or more persons are killed. According to this construction catastrophes were responsible for the loss of more than 1200 lives in the United States in 1954. Grievous as this loss may be considered it was less by a third than that of 1953, and the smallest in five years.

Two of the major catastrophes were the tandem hurricanes that spun up the coast like whirling dervishes in the late summer and early fall, causing nearly 170 fatalities in this country, to say nothing of the deaths attributed to "Hazel" in Canada. The two other major catastrophes were the crash of a military plane at Rapid City, Iowa, on August 28 and that of a scheduled passenger plane at Idlewild Airport, New York, on December 18, each of which took 26 lives.

To ameliorate somewhat the fury of the hurricanes, tornadoes, which claimed 475 victims in 1953, were comparatively innocuous in 1954. It is apparently an ill wind indeed that does not have some compensation.

The following communications are received. A new Form of Empiricism; On Innovation; On the Use of Hyposulphite of Soda in Inflammatory Rheumatism; A New Cure for Obstinate Bleeding following the Extraction of a Tooth; Report of a Singular Case of Disease, attended by Peculiar Nervous Symptoms; Laryngeal Phthisis; A Case of Placenta Praevia.

Boston M. & S. J., *March 8, 1855*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

LAROCHELLE — Fred D. LaRochelle, M.D., of Springfield, died on January 30. He was in his sixty-seventh year.

Dr. LaRochelle received his degree from Jefferson Medical College of Pennsylvania in 1911. He was founder of the Springfield Infirmary and a fellow of the American Medical Association and the Springfield Academy of Medicine.

He is survived by a daughter, a son, four sisters, a brother and nine grandchildren.

SANBORN — George P. Sanborn, M.D., of Boston and Winterport, Maine, died on February 10. He was in his eightieth year.

Dr. Sanborn received his degree from Harvard Medical School in 1901. He was a former member of the staff of the Boston City Hospital and a fellow of the American Medical Association.

He is survived by a son and a sister.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

IMMOBILIZATION TEST FOR *TREPONEMA PALLIDUM*

The Department of Public Health, through the Division of Venereal Diseases, has facilities for perform-

ing a limited number of *Treponema pallidum* immobilization tests for syphilis in selected cases for Massachusetts physicians. The test is an excellent means of distinguishing the false-positive serologic test from the positive reaction of syphilis. Therefore, it is indicated when a physician, after careful study, cannot reasonably decide whether his patient has syphilis or a biologic false-positive reaction.

Physicians requesting the test are asked to communicate directly with Dr. Nicholas J. Fiumara, director, Division of Venereal Diseases, Room 546, State House, Boston 33, Massachusetts. There is no charge for this test.

Interpretation is as follows:

A positive test means that the patient has or has had syphilis. False-positive tests are found only in yaws, pinta and bejel. In Massachusetts, however, these three diseases are imported medical curiosities.

In untreated primary syphilis the test is positive in more than 50 per cent of the patients.

In untreated secondary syphilis, it is positive in 95 to 98 per cent of the cases examined.

In untreated, acquired latent and late syphilis, as well as congenital syphilis, the test, for all practical purposes, is always positive.

In treated primary, secondary and early latent syphilis, the test, if positive, will revert to negative in an extremely high proportion. In general, the treponema-immobilizing antibody disappears from the blood as reagin does but at a slower rate and not necessarily in a parallel manner. Also, if the treponema-immobilization test was originally negative before treatment, it may never become positive after treatment has been instituted.

In treated, acquired late latent and late syphilis and in treated congenital syphilis the test, even years after treatment, remains positive in a higher proportion (85 to 95 per cent) than reagin tests. If the treponema-immobilization test becomes negative, it does so over a longer period than that required for the reversal of the reagin tests.

A negative test rules out syphilis in cases not covered by the situations enumerated above.

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR JANUARY, 1955

RÉSUMÉ

Disease	Jan. 1955	Jan. 1954	Seven-Year Median
Chancroid	4	4	4
Chicken pox	2221	1466	2322
Diphtheria	1	3	15
Dog bite	599	609	611
Dysentery, bacillary	3	60	13
Encephalitis, infectious	4	1	2
German measles	216	91	98
Gonorrhea	185	152	196
Granuloma inguinale	0	0	0
Hepatitis, infectious	160	103	7*
Lymphogranuloma venereum	4	1	1
Malaria	0	0	0
Measles	12531	97	840
Meningitis, meningococcal	13	6	7
Meningitis, Pfeiffer bacillus	9	6	6
Meningitis, pneumococcal	0	3	3
Meningitis, staphylococcal	1	0	0
Meningitis, streptococcal	0	0	0
Meningitis, undetermined	9	4	5
Mumps	1931	1811	1633
Poliomyelitis	2	10	2
Salmonellosis	14	44	4
Scarlet fever	610	487	487
Syphilis	152	239	194
Trichinosis	1	7	1
Tuberculosis, pulmonary	214	185	194
Tuberculosis, other forms	16	14	12
Typhoid fever	2	1	0
Undulant fever	0	0	1
Whooping cough	308	166	381

*Six-year median.

Comment

Diseases below the seven-year median were chicken pox, diphtheria, bacillary dysentery and whooping cough.

Only 1 case of diphtheria was reported during the month of January. This equaled the all-time low for this month, which occurred in 1953. This is encouraging when one compares this figure to that recorded in January, 1924: 1079 cases.

The situation concerning bacillary dysentery has also been encouraging in recent months. Only 3 cases were reported during January, compared with 60 for the corresponding month last year.

Diseases above the seven-year median were German measles, infectious hepatitis, measles, mumps, salmonellosis, scarlet fever and typhoid fever.

Infectious hepatitis reached a new high during the month of January, — 160 cases, — the highest figure for this month since the disease was made reportable in 1949.

The most noteworthy feature of this month's report is the 12,531 cases of measles reported — by far the highest figure for this month in the history of this state.

Geographic Distribution of Certain Diseases

The following diseases were reported from the communities named:

Diphtheria: Boston, 1.

Dysentery, amebic: Cambridge, 1; Quincy, 1; total, 2.

Dysentery, bacillary: Boston, 2; Waltham, 1; total, 3.

Encephalitis, infectious: Dracut, 1; Fitchburg, 1; Rutland, 1; Worcester, 1; total, 4.

Hepatitis, infectious: Agawam, 1; Attleboro, 1; Belchertown, 1; Boston, 7; Cambridge, 6; Chelsea Naval Hospital, 7; Chicopee, 1; East Bridgewater, 1; Fall River, 33; Fitchburg, 1; Fort Devens, 2; Framingham, 2; Haverhill, 2; Lowell, 11; Manchester, 1; Medford, 2; Millis, 1; Natick, 1; Newton, 1; Norwell, 1; Pittsfield, 3; Quincy, 1; Rockland, 1; Somerville, 3; Springfield, 11; Taunton, 2; Waltham, 44; Wellesley, 2; Westford, 1; Westport, 1; Williamstown, 1; Worcester, 7; total, 160.

Meningitis, meningococcal: Belmont, 1; Beverly, 1; Boston, 3; Holyoke, 1; Lawrence, 2; Natick, 1; New Bedford, 1; Peabody, 1; Scituate, 1; Weymouth, 1; total, 13.

Meningitis, Pfeiffer bacillus: Belmont, 1; Boston, 1; Brockton, 2; Needham, 1; Quincy, 3; Worcester, 1; total, 9.

Meningitis, staphylococcal: Clinton, 1.

Meningitis, mumps: Framingham, 1; Newton, 1; total, 2.

Meningitis, undetermined: Billerica, 1; Chelsea Naval Hospital, 1; Lexington, 1; Lowell, 1; Peabody, 1; Stoneham, 1; West Springfield, 1; Worcester, 2; total, 9.

Poliomyelitis: Fall River, 1; Shrewsbury, 1; total, 2.

Salmonellosis: Agawam, 1; Belchertown, 1; Boston, 3; Malden, 2; Melrose, 1; Newton, 1; Norwell, 1; Palmer, 1; Princeton, 1; Worcester, 2; total, 14.

Septic sore throat: Boston, 6; Bourne, 1; East Bridgewater, 1; Hardwick, 4; Quincy, 1; Watertown, 1; Worcester, 1; total, 15.

Tetanus: Haverhill, 1.

Trichinosis: West Bridgewater, 1.

Typhoid fever: New Bedford, 1; Worcester, 1; total, 2.

CORRESPONDENCE

REGARDING PRIMARY TUBERCULOSIS IN CHILDHOOD

To the Editor: We should like to reply to the editorial, "Primary Tuberculosis in Childhood," which was published in the October 21 issue of the *Journal* and which deals par-

ticularly with Dr. Edith Lincoln's proposal for a large-scale collaborative controlled study of the effectiveness of treating tuberculin converters for the prevention of development of widespread serious tuberculosis.

It appears that a major portion of the editorial is spent in opposing the treatment of tuberculin converters, and this is used as evidence against the proposal itself, which is aimed at evaluating the method. It seems clear that the suggestive results of Dr. Lincoln's study need confirmation. This evaluation is more clearly indicated since treatment of tuberculin converters is now being employed and advocated by such men as James Waring, of Denver (*Diseases of the Chest* **25**:361, 1954), George Ornstein of New York (personal communication), John Adams, of Los Angeles (personal communication), and Gardner Middlebrook, of Denver (personal communication). In fact, Dr. Adams has an ideal study in progress. A clear answer by means of some controlled study such as that proposed by Dr. Lincoln or the one now being conducted by Dr. Adams appears necessary for proper evaluation of the problem by the medical profession in general.

The objections to the treatment of tuberculin converters posed in the editorial are perhaps worthy of comment. These children might subsequently turn negative to tuberculin and thus run the possibility of later becoming reinfected, since they would be as susceptible as they were before the infection. Actually, such cases might well occur, on the basis of the experience of Dr. Middlebrook. This would not appear to be very detrimental since they would then simply resume their original state. However, the assumption of the editorial was that the source case would not be eradicated and therefore that the child might be reinfected from this source. This is an erroneous conclusion, since obviously one of the purposes of uncovering converters would be to determine where the child might have acquired his infection, — this appears to be a necessary and fruitful accompaniment to the study. The source case should be sought and treated.

The wisdom of treating converters is called into question because of reduction in the mortality to 1.5 per cent of active primary disease, the answer to which seems to be that the 1.5 per cent, if it is reducible, still represents too high a mortality from tuberculosis and that this program offers a possibility for completely eliminating the mortality among those recently infected.

A suggested program of better and more effective case finding and follow-up study to detect cases thoroughly has not been outlined, and there appears to be no reason why the two programs are mutually exclusive; indeed, they might well supplement each other.

If treatment is to be limited to those with early active disease the very group in which the mortality is highest — namely, those with meningitis — will be missed. These cases are often not evident until the meningitis is well developed and the miliary character well established.

The assumption that one might have to treat a great majority of the young population appears to be entirely fallacious. Actually, the conversion rate based on actual observations in areas where this has been attempted runs less than 1 per cent per year — that is, 1 out of every 100 children might be subject to treatment at the time at which he converted. This treatment does not seem to be very tedious, entailing the daily use of some simple drug such as INH.

This new and imaginative approach should not be so lightly disparaged, but rather tested in the cold light of a controlled study to the eventual benefit of all.

MICHAEL L. FURCOLOW, M.D., Kansas City, Kansas
J. ARTHUR MYERS, M.D., Minneapolis, Minnesota

Note: The major portion of the editorial mentioned was devoted to a presentation of Dr. Lincoln's very creditable long-term study of tuberculosis in childhood. Only part of the last paragraph mentioned, by way of comment, some points that, it was believed, should be considered in undertaking the proposed program of isoniazid treatment of tuberculin converters who have no evidence of clinically active disease. The editor is pleased to present the correspondents' comments on these points. Any well conceived and well controlled study that is undertaken with a full understanding of the problems involved and has as its objective a reduction in mortality from tuberculosis is heartily endorsed rather than disparaged. Dr. Lincoln's proposed study is obviously well conceived, and the pre-eminence of the participating investigators assures a carefully controlled trial that should, in time, yield the answer to the major question that has been set and should also reveal any difficulties involved in the proposed regimen.—ED.

NOTICES

SOUTH END MEDICAL CLUB

A meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on March 15 at noon. Dr. J. Englebert Dunphy will speak on the topic "Management of Advanced and Inoperable Cancer."

NORFOLK DISTRICT MEDICAL SOCIETY

A meeting of the Norfolk District Medical Society will be held in the auditorium of the Jimmy Fund Building, 35 Binney Street, Boston, on March 22 at 8:15 p.m. Drs. Carter R. Rowe, Thomas B. Quigley and Meier G. Karp will speak on the topic "Orthopedic Problems in General Practice."

PEDIATRIC SEMINAR

A pediatric seminar will be presented by the Children's Medical Service and associates, Massachusetts General Hospital, in the lower outpatient amphitheater of the hospital on March 9 at 7:30 p.m. Drs. Raymond D. Adams and Gaston E. Blom and Miss Elizabeth White, Massachusetts General Hospital, and Dr. Herman Yannet, Southbury Training School, will discuss the topic "Appraisal and Management of Mentally Handicapped Children." All interested physicians are invited.

AERO MEDICAL ASSOCIATION

There will be a special session on space medicine at the meeting of the Aero Medical Association, Hotel Statler, Washington, D.C., March 21 through 23. The other topics will be related to the physiologic, medical, mechanical and physical aspects of aviation medicine.

MASSACHUSETTS ACADEMY OF GENERAL PRACTICE

The spring clinical assembly of the Massachusetts Academy of General Practice will be held in Thayer Hall Auditorium, Worcester City Hospital (morning session), and at the Bancroft Hotel (afternoon and evening sessions), Worcester, on March 5. The program is as follows:

9:00 a.m. Clinical presentations arranged by Dr. Henry S.M. Uhl.
12:00 m.-2:00 p.m. Registration and luncheon.
2:00 p.m. The Intensive Treatment of Refractory Congestive Heart Failure. Dr. Henry S.M. Uhl.
2:20 p.m. Specific Indications for the Use of Adrenal Steroids and ACTH in Clinical Medicine. Dr. Raymond S. Butler.
2:40 p.m. Management of Dysmenorrhea. Dr. Raymond F. Sullivan.
3:00 p.m. Lung Cancer: The problem of early diagnosis. (Film.)
3:30 p.m. Drug Allergy. Dr. Ethan Allan Brown.
4:00 p.m. Gynecologic Diagnosis for Office Procedures. Dr. Christopher J. Duncan.
5:30-7:30 p.m. Cocktails, dinner and dancing.
7:30 p.m. Business meeting.
8:00 p.m. Dr. Theodore G. Klumpp, president, Winthrop-Stearns.

AMERICAN HEART ASSOCIATION

A New York and New England regional conference of the American Heart Association will be held at the Northfield Hotel, East Northfield, Massachusetts, April 6 and 7. Room reservations may be made through Charles A. Gates, Massachusetts Heart Association, 650 Beacon Street, Boston 15.

RADCLIFFE COLLEGE FELLOWSHIP

Radcliffe College announces the eleventh annual Helen Putnam Fellowship for Advanced Research — with research facilities at Harvard University — for women doing postdoctoral work in the fields related to human genetics or mental health, including psychology, child development and other areas of social science. The grant is $3000 a year, with the possibility of renewal; preference will be given to students whose work is in progress. Applications should be sent to the secretary, Graduate School, Radcliffe College, Cambridge 38, Massachusetts, before April 1.

AMERICAN CANCER SOCIETY FELLOWSHIPS YALE UNIVERSITY

Several predoctoral and postdoctoral fellowships, supported by a grant from the American Cancer Society, are being offered at Yale University Graduate School to promote training and research in statistical methods as applied to the design of experiments and the collection and analysis of data applicable to the study of growth, typical or malignant, the epidemiology of cancer and other chronic diseases and clinical research in cancer.

Applicants for the predoctoral fellowships are expected to enter the Graduate School as candidates for the degree of Doctor of Philosophy and will be given training in biology and statistics. The fellowships are awarded for three years, at $2000 a year.

Applicants for the postdoctoral fellowships must possess the degree of Doctor of Medicine, Philosophy or Science, and will receive training in biometry, biostatistics and related subjects. Fellowships are awarded for one year and may be renewed for two additional years, at $3000 to $4500 a year.

Further information may be obtained from Professor E. Cuyler Hammond, director of graduate studies in biometry, 30 Hillhouse Avenue, Yale University, New Haven, Connecticut.

UNITED STATES PUBLIC HEALTH SERVICE EXAMINATION FOR NURSE OFFICERS

A competitive examination for appointment of nurse officers to the regular corps of the United States Public Health Service will be held at various centers throughout the United States from April 26 through 28. Applications must be received before April 4.

SOCIETY MEETINGS AND CONFERENCES

March–April. Postgraduate Medical Institute. Page 451, issue of September 9.
March–May. Sanitary Engineering Center Training Programs. Page 122, issue of July 15.
March 1–May 9. Seminar in Psychiatry and Neurosurgery. Page 452, issue of September 9.
March 4–30. Consultation Clinics for Crippled Children in Massachusetts. Page 328, issue of February 24.
March 5. Massachusetts Academy of General Practice. Spring Clinical Assembly, Worcester.
March 5. Massachusetts Academy of General Practice. Page 371.
March 5–May 7. Middlesex South District Medical Society. Postgraduate Course. Page 758, issue of October 28.
March 7. New England Cardiovascular Society. Page 329, issue of February 24.
March 7–12. Course in Care of Atomic Casualties. Page 285, issue of August 12.
March 8. Harvard Medical Society. Page 329, issue of February 24.
March 9. Pediatric Seminar. Page 371.
March 11 and 25. Postgraduate Course in Occupational Medicine. Page 922, issue of November 25.
March 15. South End Medical Club. Page 371.
March 21–23. Aero Medical Club. Page 371.
March 21–April 18. Hartford Medical Society. Page 289, issue of February 17.
March 22. Norfolk District Medical Society. Page 371.
March 23–26. International Academy of Proctology. Page 876, issue of November 18.
April 1. American Psychiatric Association (Massachusetts District Branch). Page 289, issue of February 17.
April 1. New England Society of Anesthesiologists. Page 289, issue of February 17.
April 5. Microcirculatory Conference. Page 289, issue of February 17.
April 6 and 7. American Heart Association. Page 371.
April 7–9. Postgraduate Course in Obstetrics and Pediatrics. Page 329, issue of February 24.
April 8. Massachusetts Society for Research in Psychiatry. Page 679, issue of October 14.
April 13. Chelsea Soldiers' Home. Page 329, issue of February 24.
April 13. New England Surgical Society. Spring Meeting. Massachusetts Memorial Hospitals and Boston University School of Medicine.
April 21 and 22. New York Academy of Medicine (Eastern States Health-Education Conference). Page 922, issue of November 25.
April 28–30. American Goiter Association. Page 329, issue of February 24.
April 30. State University College of Medicine at New York City. Page 289, issue of February 17.
May 4 and 5. American Psychosomatic Society. Page 286, issue of August 12.
May 17–19. Massachusetts Medical Society. Annual Meeting. Hotel Statler, Boston.
June 5 and 6. American Board of Physical Medicine and Rehabilitation. Page 794, issue of November 4.
June 21–25. National Association for the Prevention of Tuberculosis. Page 540, issue of March 25.
August 28–September 2. American Congress of Physical Medicine and Rehabilitation. Page 157, issue of January 27.
November 6–13. Second International Congress of Allergology. Page 157, issue of January 27.
November 29–December 2. Interim Session of the American Medical Association. Boston.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, MARCH 10

THURSDAY, MARCH 10

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Experiences with Billroth No. 1 in Resection in Treatment of Peptic Ulcer. Dr. Donald V. Baker, Jr. Veterans Administration, Boston Outpatient Clinic, 17 Court Street.
*11:00 a.m.–12:00 m. Thoracic Conference. Atrial Septal Defects. Drs. Lewis Dexter and Dwight Harken. Main Amphitheater, Peter Bent Brigham Hospital.
*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital. Cambridge.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:00 m.–1:00 p.m. Surgical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*12:00 m.–1:00 p.m. Ammonia Intoxication in Liver Disease and Portacaval Shunts. Dr. William V. McDermott. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Orthopedic Clinic. Amphitheater, Peter Bent Brigham Hospital.
*4:00–5:00 p.m. Pediatric Seminar. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*4:30–5:30 p.m. Trauma to Main and Spinal Cord. Dr. Joseph Dorsey. Auditorium, Nurses' Home, Cambridge City Hospital, 1493 Cambridge Street, Cambridge.
*5:00 p.m. Case Presentation and Pathological Discussion Followed by a Subject of Special Presentation. Joslin Auditorium, New England Deaconess Hospital.

FRIDAY, MARCH 11

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–1:00 p.m. Medical Grand Rounds. Dr. Proger and Staff. Stearns Auditorium, New England Center Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*4:00–5:00 p.m. Child Psychiatry. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*4:00–6:00 p.m. X-Ray Conference. Dr. Merrill Sosman. Stearns Auditorium, New England Center Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.

SATURDAY, MARCH 12

*8:00–8:45 a.m. Case Presentation. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Anesthesia Conference. Dr. Etsten. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*9:00–10:30 a.m. Surgical Grand Rounds. Dr. Child and Staff. Stearns Auditorium, New England Center Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*10:30 a.m.–12:00 m. Surgical History Meeting. Stearns Auditorium, New England Center Hospital.
*11:00 a.m.–12:00 m. Hematology Clinic. Dr. William Dameshek. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.

(Concluded on page xxviii)

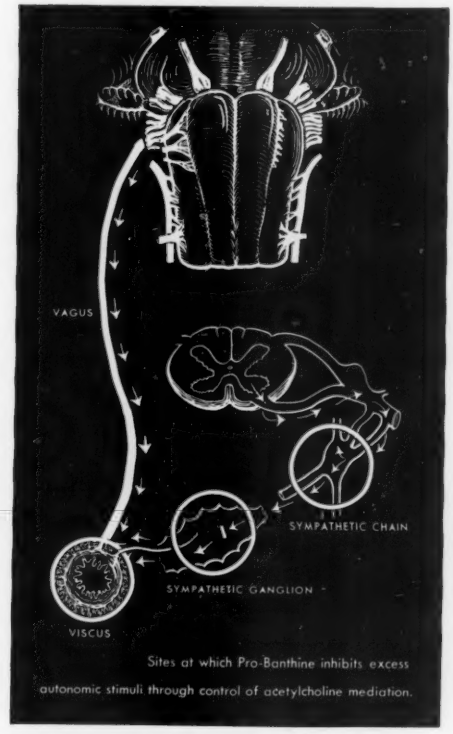
PRO-BANTHINE® FOR ANTICHOLINERGIC ACTION

A Combined Neuro-Effector and Ganglion Inhibitor

Pro-Banthine consistently controls gastrointestinal hypermotility and spasm and the attendant symptoms.

Pro-Banthine is an improved anticholinergic compound. Its unique pharmacologic properties are a decided advance in the control of the most common symptoms of smooth muscle spasm in all segments of the gastrointestinal tract.

By controlling excess motility of the gastrointestinal tract, Pro-Banthine has found wide use[1] in the treatment of peptic ulcer, functional diarrheas, regional enteritis and ulcerative colitis. It is also valuable in the treatment of pylorospasm and spasm of the sphincter of Oddi.



Sites at which Pro-Banthine inhibits excess autonomic stimuli through control of acetylcholine mediation.

Roback and Beal[2] found that Pro-Banthine orally was an "inhibitor of spontaneous and histamine-stimulated gastric secretion" which "resulted in marked and prolonged inhibition of the motility of the stomach, jejunum, and colon. . . ."

Therapy with Pro-Banthine is remarkably free from reactions associated with parasympathetic inhibition. Dryness of the mouth and blurred vision are much less common with Pro-Banthine than with other potent anticholinergic agents.

In Roback and Beal's[2] series "Side effects were almost entirely absent in single doses of 30 or 40 mg. . . ."

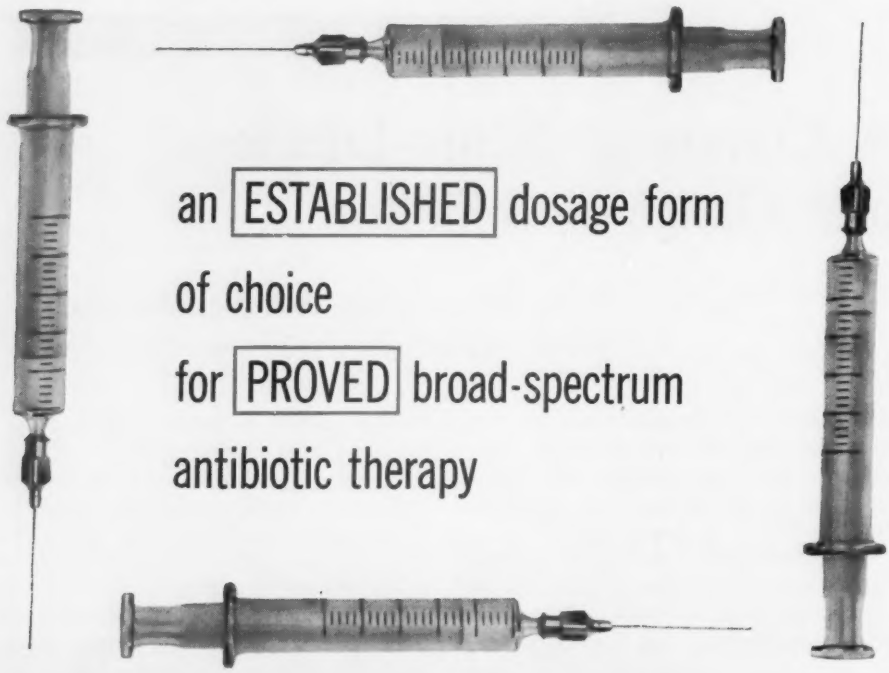
Pro-Banthine (β-diisopropylaminoethyl xanthene-9-carboxylate methobromide, brand of propantheline bromide) is available in three dosage forms: sugar-coated tablets of 15 mg.; sugar-coated tablets of 15 mg. of Pro-Banthine with 15 mg. of phenobarbital, for use when anxiety and tension are complicating factors; ampuls of 30 mg., for more rapid effects and in instances when oral medication is impractical or impossible.

For the average patient one tablet of Pro-Banthine (15 mg.) with each meal and two tablets (30 mg.) at bedtime will be adequate. G. D. Searle & Co., Research in the Service of Medicine.

1. Schwartz I. R.; Lehman, E.; Ostrove, R., and Seibel, J. M.: Gastroenterology *25*:416 (Nov.) 1953.

2. Roback, R. A., and Beal, J. M.: Gastroenterology *25*:24 (Sept.) 1953.

SEARLE



an ESTABLISHED dosage form
of choice
for PROVED broad-spectrum
antibiotic therapy

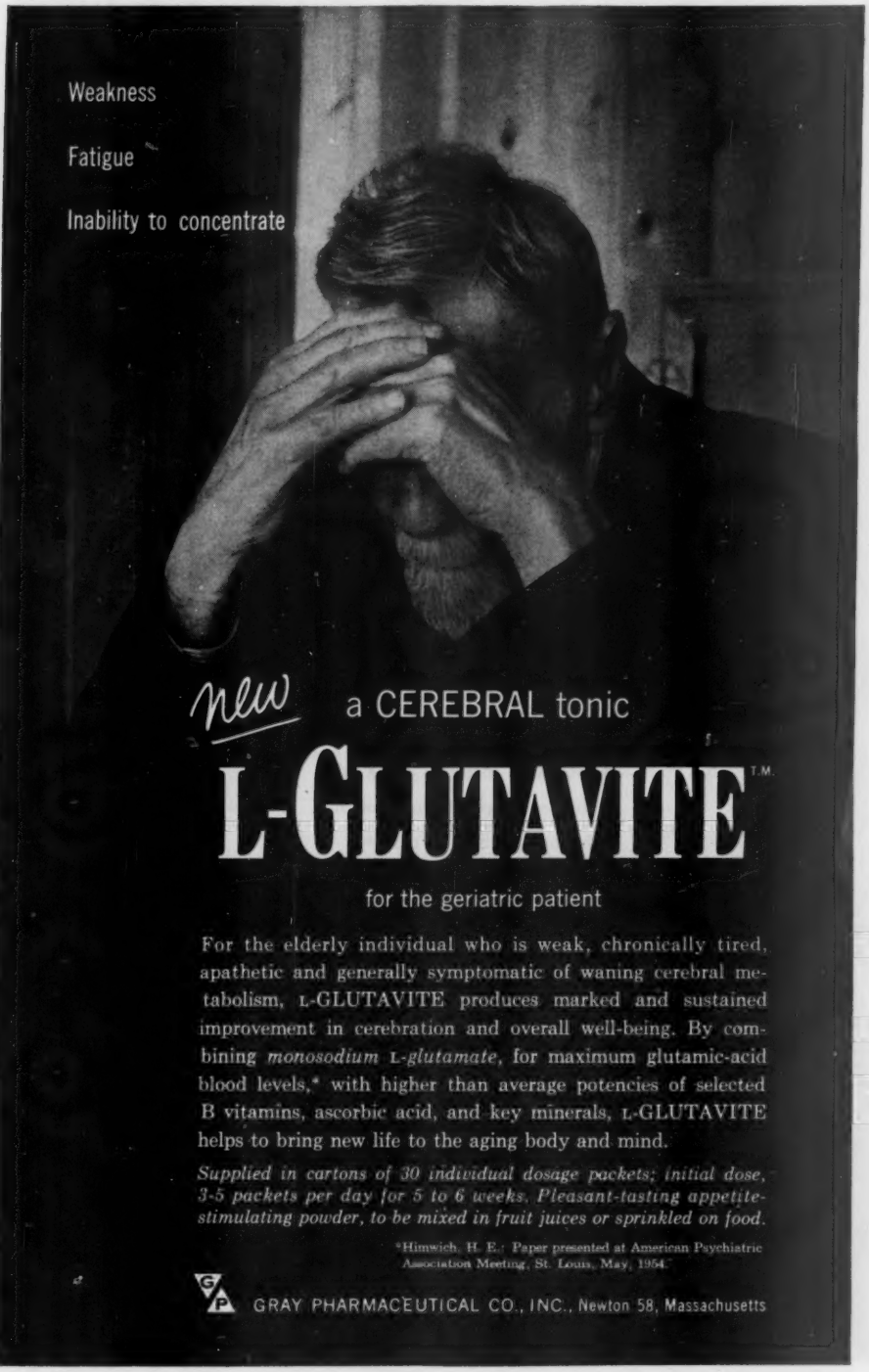
TERRAMYCIN®
Brand of oxytetracycline
INTRAMUSCULAR

the *first* broad-spectrum antibiotic
available in this convenient parenteral form
for the treatment of a wide range
of infections due to susceptible organisms.

Supplied in single-dose vials. On reconstitution,
each single dose contains: Crystalline
Terramycin hydrochloride—100 mg.
Magnesium chloride—5%
Procaine hydrochloride—2%

Pfizer

PFIZER LABORATORIES, *Brooklyn 6, N. Y.*
Division, Chas. Pfizer & Co., Inc.



new a CEREBRAL tonic

L-GLUTAVITE™

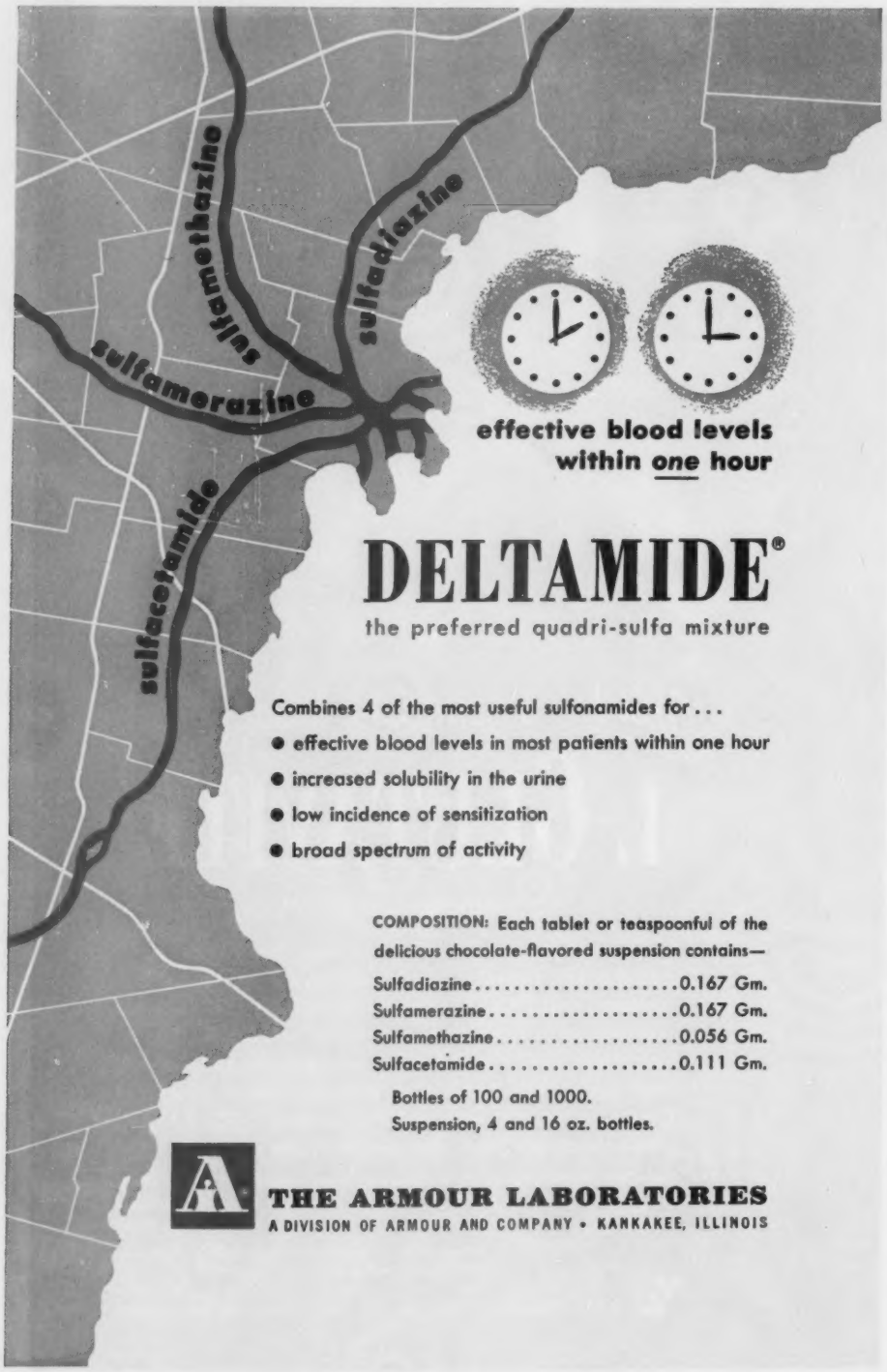
for the geriatric patient

For the elderly individual who is weak, chronically tired, apathetic and generally symptomatic of waning cerebral metabolism, L-GLUTAVITE produces marked and sustained improvement in cerebration and overall well-being. By combining *monosodium L-glutamate*, for maximum glutamic-acid blood levels,* with higher than average potencies of selected B vitamins, ascorbic acid, and key minerals, L-GLUTAVITE helps to bring new life to the aging body and mind.

Supplied in cartons of 30 individual dosage packets; initial dose, 3-5 packets per day for 5 to 6 weeks. Pleasant-tasting appetite-stimulating powder, to be mixed in fruit juices or sprinkled on food.

*Himwich, H. E.: Paper presented at American Psychiatric Association Meeting, St. Louis, May, 1954.

GRAY PHARMACEUTICAL CO., INC., Newton 58, Massachusetts



effective blood levels
within one hour

DELTAMIDE®

the preferred quadri-sulfa mixture

Combines 4 of the most useful sulfonamides for . . .

- effective blood levels in most patients within one hour
- increased solubility in the urine
- low incidence of sensitization
- broad spectrum of activity

COMPOSITION: Each tablet or teaspoonful of the delicious chocolate-flavored suspension contains—

Sulfadiazine	0.167 Gm.
Sulfamerazine	0.167 Gm.
Sulfamethazine	0.056 Gm.
Sulfacetamide	0.111 Gm.

Bottles of 100 and 1000.
Suspension, 4 and 16 oz. bottles.

THE ARMOUR LABORATORIES
A DIVISION OF ARMOUR AND COMPANY • KANKAKEE, ILLINOIS

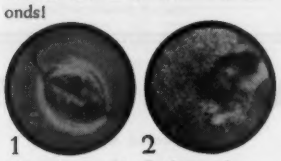
DAVIS TECHNIC
FOR
VAGINAL TRICHOMONIASIS

EXPLODES TRICHOMONADS

WITHIN 15 SECONDS

VAGISEC, a new agent for the treatment of vaginal trichomoniasis, was originated as "Carlendacide" by Dr. Carl Henry Davis, well-known gynecologist and C. G. Grand, research physiologist.

Vagisec's triple action kills trichomonads within 15 seconds of contact. Its unique synergism "captures" calcium, removes lipid materials, and literally explodes the trichomonad — all within 15 seconds!



1 *Microphotograph (phase contrast microscope) of a Trichomonas vaginalis*

2 *Trichomonad "exploded" within 15 seconds of contact with* VAGISEC *liquid as used in douche*

Debris and mucus hide trichomonads. Trichomonads do not exist in vaginal secretion alone. They are vigorously motile and burrow deeply into the surface of the vaginal mucosa, covered by cellular debris and mucus. Vagisec penetrates this protection by lowering surface tension. It penetrates into the folds of the vaginal mucosa.

Vagisec attacks three ways. The chelating agent in Vagisec attaches itself to the calcium of the calcium proteinate, weakening the surface of the trichomonad. The wetting agent in Vagisec removes waxes and lipid materials from its surface, allowing the detergent in Vagisec to move into the cell, breaking up its structure by denaturing the protein. Then water moves in and blows up the trichomonad.

No other agent or combination of agents kills the trichomonad in this specific fashion, or with the speed of Vagisec.

Result of intensive research. Davis and Grand made studies[1] of commonly used trichomonacides. They showed that most antiseptics coagulated albuminous material, which protects trichomonads.

They realized that a satisfactory trichomonacide had to penetrate and dissolve mucinous material. It had to be non-irritating to the already inflamed mucosa and lethal to the trichomonad on brief contact.

Based on these concepts, an exhaustive study[2] of all available new trichomonacidal agents resulted in the development and patenting of "Carlendacide." Clinically tested, "Carlendacide" proved to be a remarkably fast-acting, effective treatment for vaginal trichomoniasis. Dr. Davis recommends a combination of office treatment and home treatment, the Davis technic.

Office treatment. The vagina is exposed with a speculum. The walls of the vagina are wiped dry with cotton sponges and then thoroughly washed with a 1:250 dilution of Vagisec. (Thorough washing takes about three minutes.) The vagina is then dried with cotton sponges. The patient can leave the office without a tampon, or messy discharge or staining.

A minimum of six office treatments are recommended: three the first week, two the second, and one the third week.

Home treatment. Both VAGISEC liquid and VAGISEC jelly should be prescribed for home treatment. Have the patient insert VAGISEC jelly each night and douche with VAGISEC liquid (1 teaspoon to a quart of warm water) each morning except on days she receives treatment at the office. This treatment should continue through two menstrual periods. Four weeks after treatment, the douche should be omitted at least three days and the patient re-examined.

Afterwards, the patient should continue douching with Vagisec at least two or three times each week as a precaution against re-infection.

Summary. Vagisec kills trichomonads in 15 seconds. Failure due to lack of penetration is eliminated. Vagisec is non-toxic and leaves no discoloration or messy discharge. The Davis technic is a triple attack of Vagisec office treatment, home treatment, and Vagisec jelly. Vagisec has been clinically tested and proved as a remarkably fast-acting, effective treatment for vaginal trichomoniasis.

References: 1. Davis, C. H.: J.A.M.A. *92*:306, 1929. 2. Davis, C. H.: Am. J. Obst. & Gynec. *68*:559 (Aug.) 1954.

JULIUS SCHMID, INC., *gynecological division* 423 West 55th Street, New York 19, N. Y.

VAGISEC IS THE TRADE-MARK OF JULIUS SCHMID, INC., FOR PRODUCTS TO BE USED IN THE CONTROL OF VAGINAL TRICHOMONIASIS

For optimum results
in teen-age
dysmenorrhea

always prescribe
2
Edrisal* tablets
per dose

Smith, Kline & French
Laboratories, Philadelphia

Each 'Edrisal' tablet contains 'Benzedrine' Sulfate (racemic amphetamine sulfate, S.K.F.), 2.5 mg.; acetylsalicylic acid, 2½ gr. (0.16 Gm.); phenacetin, 2½ gr. (0.16 Gm.). Available on prescription only.
*T.M. Reg. U.S. Pat. Off.

DOCTOR!

YOU may be spending too much for INSURANCE!

There may be dangerous gaps in the insurance you now carry that can result in great losses. Some coverage may even be uncollectible! These, and other important insurance problems can be solved for you by the Liner Counselling Division. We act entirely in your interests without pressure of soliciting your insurance business . . . give advice that cuts your premiums in 6 out of 10 cases, strengthens protection against losses!

Write, wire or phone for details

JOHN LINER AND Company
COUNSELLING DIV.

Analysis Only
No Soliciting

334 Boylston St., Boston • CO 7-6001
Licensed Insurance Counsellors to Industry

FRACTURE COURSE

Conducted by

Philadelphia Regional Committee on Trauma

of

American College of Surgeons

APRIL 21, 22, 23, 1955

College of Physicians of Philadelphia —
19 So. 22nd Street

GUEST LECTURERS

DR. LORENZ BOHLER, VIENNA, AUSTRIA

and

DR. JORG BOHLER, LINZ, AUSTRIA

Discussions by Outstanding American Fracture Surgeons

FEE: Practicing Physicians — $50.00
Residents, Interns and Medical Students—$25.00

Application blanks may be secured by writing to
William T. Fitts, Jr., M.D., 301 So. 21st Street,
Philadelphia 3, Pa.

Enrollment limited to 400 persons

POST-GRADUATE COURSE IN SURGERY

Designed for candidates for the F.R.C.S.(C) and the American Board of Surgery

The Surgical Staff of the Royal Victoria Hospital is conducting its tenth annual course in surgery designed especially for those wishing to write the F.R.C.S.(C) and the American Board of Surgery.

The course consists of two sections; the correspondence portion will commence on May 1 and will consist of selected reading with weekly written questions. The clinical and didactic full-time course will be held at the Hospital in mid-August and will last 7 weeks.

All the required work will be presented by the various specialists and will consist of physiology, anatomy, pathology, x-ray in association with general and special surgery.

Fee for the course $225.00

Address applications or inquiries to:

The Post-Graduate Board
ROYAL VICTORIA HOSPITAL
MONTREAL 2, P.Q.

J.S. WATERMAN & SONS
SINCE 1832
FUNERAL SERVICE

LOCAL and DISTANT

GREATER BOSTON SINCE 1832

correct chronic anemia

Unexplained weakness, easy fatigability, pallor, palpitation, and dyspnea on exertion ordinarily are the tell-tale signs of a chronic anemia in women during the third to fifth decades.[1]

1. Rath, C. E.: M. Clin. North America 34: 1779, 1950.

armatinic®
activated

When you prescribe Armatinic Activated you give exceptionally effective potencies of all hematopoietic factors which combat both macrocytic and microcytic anemias.

Each Armatinic Activated Capsulette contains:

Ferrous Sulfate Exsiccated	200 mg.
Vitamin B_{12}	10 mcg.
Folic Acid	1 mg.
Vitamin C	50 mg.
Liver Fraction 2 N.F. with Duodenum (contains Intrinsic Factor)	350 mg.

Average adult dose: 3 capsulettes daily. Bottles of 100 and 1000.

THE ARMOUR LABORATORIES
A DIVISION OF ARMOUR AND COMPANY
KANKAKEE, ILLINOIS

ELECTROENCEPHALOGRAPHIC LABORATORY, INC.
270 Commonwealth Ave., Boston KE 6-8100
Electroencephalograms
Electromyograms

PHYSICIANS' Office FURNITURE. All standard lines, new. Used equipment from time to time. Convenient terms. Visit our showroom close by Veterans Hospital. Ample parking. T. J. NOONAN Co., 408 South Huntington Avenue, Jamaica Plain (Boston 30), Mass. Phone JAmaica 2-8700 for literature. Medical, hospital, laboratory, sickroom supplies. B260-20-tf

TWO MEDICAL RESIDENCIES, at the third year level, available July 1, 1955 in a four year AMA approved program leading to Board certification. Write: Executive Vice-President, The Roosevelt Hospital, 428 West 59th Street, New York 19, N. Y. B189-3-tf

RESIDENCIES AVAILABLE—Veterans Administration Hospital. Large southern medical center, affiliated with Tulane and Louisiana State University Schools of Medicine. Fully approved. Openings July 1, 1955 in Internal Medicine, General Surgery, Urology, Ophthalmology, Pathology and Psychiatry. Apply — Dr. W. W. Frye, Chairman, Deans Committee, 1542 Tulane Avenue, New Orleans, Louisiana. B194-5-13t

OPENING for 1 resident at the Gaston Hospital, Dallas, Texas. Approved by American Board for 1 year general surgery. Salary $200.00 per month and complete maintenance. B30-11-tf

FOR SALE—New six-room house with doctor's office in growing town of 5000, 12 miles from Boston. Part or full-time general practice. One M.D. in area. Address A190, *New Eng. J. Med.* 8-3t

WANTED—PHYSICIAN—Full-time. General duties in private psychiatric hospital. Psychiatric training not essential. Bournewood Hospital, 300 South Street, Brookline. Phone Charles Saltzman, M.D., HOmestead 9-0300. B198-7-3t

WELLESLEY—Colonial home suitable for doctor. Fine condition, excellent location. WEllesley 5-4087. B205-9-13t

FOR RENT—Very desirable, spacious medical office in professional building on Beacon Street, Boston. 24-hour switchboard service. Rent very reasonable. BLue Hills 8-8988. B206-9-4t

BIND your *New England Journal of Medicine*. Make it a permanent part of your library—for easy reference and lasting wear. In full black library buckram, only $3.30 per volume, plus shipping charges. All other journals and periodicals bound also. Inquiries invited. Norden Bindery, 2100 West Grand Avenue, Chicago 12, Ill. B300-14-tf

UNITED LIMB & BRACE CO., Inc., manufacturers of artificial limbs. 61 Hanover Street, Boston, CA 7-2183. B517-6-tf

OFFICE FURNITURE—New—Used—Refinished. Bought and sold. Desk Clearing House, 115 Broad Street, Boston. HU 2-1318. B72-22-tf

WANTED—Young man as assistant in General Practice in Boston suburb with view toward eventual partnership. Give full details of training and requirements. Address A191, *New Eng. J. Med.* 8-4t

COLONIC IRRIGATIONS, massage, diathermy. Beatrice M. Woods, 511 Beacon Street, Boston, CO 6-8722. B80-16-tf

DOCTOR'S SUITE ON FIRST FLOOR — Partly furnished if desired. Commonwealth Avenue near Dartmouth Street. KE 6-9230. B340-19-tf

RADIOLOGIST — Opportunity for young recent graduate to affiliate with two other radiologists in Boston practice, office and hospital. Permanent association possible, depending on ability, and so forth. Address A183, *New Eng. J. Med.* 6-4t

DOCTORS AND DENTISTS — For rent, fine residential home. Best professional location, Medford. First floor, three rooms, laboratory. MYstic 8-6118. B201-8-3t

NISSEN'S INSTITUTE OF PHYSICAL THERAPY, 1126 Boylston Street, Boston, KE 6-1030. Cape Cod office, Route 28, West Harwich. Telephone Harwich 984. B290-3-tf

FOR SALE—General Practice—8-room house, 4-room office, (fully equipped). Two general hospitals within 4 miles. Population, 10,500. Area within 20 miles of Boston. Leaving to specialize. Address A193, *New Eng. J. Med.* 9-3t

MEDICAL STUDENT desires part-time hospital position in clinical or laboratory work, for room, board and salary. Boston or vicinity. Address A192, *New Eng. J. Med.* 9-1t

STORROW HOUSE
(Former Storrow Estate at Lincoln, Mass.)
Staffed and Operated by the MASSACHUSETTS GENERAL HOSPITAL
For nonpsychiatric ambulatory and semi-ambulatory patients needing rest or convalescent facilities.
CHARGES: $7.00 to $10.00 per day
Transportation for visits to physician's office provided. For information, call LIncoln 6-0343 or Massachusetts General Hospital Admitting Office LA 3-8200.

BOARD INTERNIST, special training Cardiology, Harvard graduate, Boston-trained, desires association with practicing internist or group in New England, New York, New Jersey or Pennsylvania. Address A188, *New Eng. J. Med.* 7-3t

INTERNIST — Board eligible, university trained, married, age 30, due out of Navy early spring, desires position with established internist, or group, preferably in Northeast. Address A175, *New Eng. J. Med.* 4-tf

FOR RENT—Former physician's office in City of Woburn. Population—25,000 with no resident pediatrician. Excellent opportunity for young man. Also good spot for general practitioner. Ample parking facilities. Contact Dr. Thomas J. Jones, D.D.S., Caulifield Building, 14 Church Avenue, Woburn, Massachusetts. B184-2-8t

4-ROOM DOCTOR'S OFFICE completely equipped. Air conditioned. Excellent location in West Medford. Address A172, *New Eng. J. Med.* 3-eow-tf

USED instruments and equipment bought and sold. All types of repairs reasonably done. GALE SURGICAL SUPPLY CO., 6 Francis Street, Boston. (Opposite Peter Bent Brigham Hospital) AS 7-0777. B166-22-eow-tf

OUR FAMILY TREE is the ideal book in which to record Your Family Tree. Send for illustrated circular to Wilder's Genealogical Bookshop, Somerville 43, Massachusetts. Specialists since 1905 in genealogical publications and family information. B203-9-1t

WANTED—RESIDENT PHYSICIAN—Position open July 1, 1955. Grand opportunity for young man who has just completed his internship or residency. General hospital, 142 beds and organized medical staff, 50 physicians. Applications accepted for 1 year or longer as individual desires. Starting salary $3,200 per annum. Desirable opening with close association with medical profession of community. Apply: Matthew I. Barron, Director, Portland City Hospital, Portland, Maine. Interview granted at applicant's convenience. B204-9-8t

Founded 1879

RING SANATORIUM

EIGHT MILES FROM BOSTON

For the study, care and treatment of emotional, mental, personality and habit disorders.

On a foundation of dynamic psychotherapy all other recognized therapies are used as indicated.

Cottage accommodations meet varied individual needs. Limited facilities for the continued care of progressive disorders requiring psychiatric, medical, or neurological supervision.

Full resident and associate staff. Courtesy privileges to qualified physicians.

BENJAMIN SIMON, M.D.
Director

CHARLES E. WHITE, M.D.
Assistant Director

Arlington Heights
Massachusetts
ARlington 5-0081

Woodside Cottages

FRAMINGHAM, MASS.

A sanitarium specially adapted for nervous and convalescent patients who need rest and upbuilding in normal surroundings.
No committed mental cases.

ARTHUR H. WARD, M.D., *Medical Director*

GLENSIDE

JAMAICA PLAIN, BOSTON, MASS.

A small, attractively located sanitarium for nervous, mild mental or chronic illnesses.

6 Parley Vale Tel. JA 4-0044

BALDPATE, Inc.

GEORGETOWN, MASSACHUSETTS

Telephone GEO 2131

LOCATED IN THE HILLS OF ESSEX COUNTY
30 miles north of Boston

For the treatment of psychoneuroses, personality disorders, psychoses, alcoholism and drug addiction.

Psychotherapy is the basis of treatment; electric shock treatments, subcoma and deep coma insulin therapy when indicated; sleep treatment for withdrawal of narcotics.

Occupation under a trained therapist, diversions and outdoor activities.

G. M. SCHLOMER, M.D.
Medical Director

Wiswall Sanatorium

203 GROVE ST., WELLESLEY, MASS.
For the care of mild mental and nervous patients in country surroundings. Small grouping allows a homelike atmosphere and personal contact.
E. H. WISWALL, M.D., *Superintendent*
HALE POWERS, M.D., *Medical Director*
Tel. WE 5-0261

PROTEIN BOUND IODINE
TOTAL IODINE
FLAME PHOTOMETRY
Immediate Service
BOSTON MEDICAL LABORATORY
NORBERT BENOTTI — JOSEPH BENOTTI
Directors
19 BAY STATE ROAD, BOSTON 15, MASS.
KE 6-0348 and 0533

DAVID MEMORIAL NURSING HOME

BROOKLINE 46, MASS.
S. D. COHEN, R.N., *Supt.*
Convalescents — Invalid-Elderly
Accepted by Blue Cross - Blue Shield Prolonged Illness Program
61 Park Street BE 2-3530

HANOVER HOUSE, INC.

West Hanover, Mass.

A sanatorium in the South Shore Area within easy distance from Boston.

Tel. Rockland 1690 — Quincy Office PR 3-6930

For the diagnosis and treatment of neurological diseases, emotional disturbances and personality disorders. All modern forms of specialized therapy (including electroshock) with emphasis on psychotherapy; treatment of alcoholism and related addictions on most modern, scientifically approved basis. Unusually attractive atmosphere, singularly free from "institutionalization."

Excellent nursing and medical care for limited number of chronic patients.

No committed patients.

Outpatient treatments for referred cases only.

ELSIE S. NEUSTADT, M.D., *Medical Director*
RUDOLPH NEUSTADT, M.D., *Clinical Director*

PERKINS SCHOOL

LANCASTER, MASS.

Devoted to the scientific understanding and education of children of retarded development. Five homelike and attractive buildings surrounded by 85 acres of campus and gardens.

FRANKLIN H. PERKINS, M.D.

Washingtonian Hospital

41 MORTON STREET, BOSTON 30, (Jamaica Plain) MASS.
Incorporated 1859

Conditioned Response, Psychotherapy, Antabuse, Adrenal Cortex and other drugs, Semi-Hospitalization for Rehabilitation of Male and Female Alcoholics

Treatment of Acute Intoxication and Alcoholic Psychoses Included

State Outpatient Clinic and Social Service Department for Male and Female Patients

JOSEPH THIMANN, M.D., *Medical Director*
Consultants in Medicine, Surgery and the Other Specialties
Telephone JA 4-1540

DELINQUENT ACCOUNTS
COLLECTED

Ethically — Courteously — Efficiently

Experienced Over 25 Years

Monthly Report Bonded

For particulars call or write

Medical Clearing Bureau, Inc.

110 Tremont Street, Boston, Mass.
HU 2-5570

Index to Advertisers

	PAGE
American College of Surgeons	xxiv
The Armour Laboratories	xxii, xxv
Baldpate, Inc.	xxvii
Boston Medical Laboratory	xxvii
Ciba Pharmaceutical Products, Inc.	xxix, Back Cover
David Memorial Nursing Home	xxvii
Davies, Rose & Company, Ltd.	xvi
Electroencephalographic Laboratory, Inc.	xxvi
Endo Products, Inc.	xxxi
Ethicon, Inc.	After xxviii
Fine Chemicals	xxx
Glenside, Inc.	xxvii
Gray Pharmaceutical Co., Inc.	xxi
Hanover House, Inc.	xxvii
Hoffmann-La Roche, Inc.	After xiv
Ives-Cameron Company	xxxii
Lederle Laboratories	x, xi
Thos. Leeming & Co., Inc.	xxviii
Eli Lilly and Company	xviii
John Liner and Company	xxiv
Medical Clearing Bureau, Inc.	xxvii
The Wm. S. Merrell Company	xii
William Morrow and Company, Inc.	xxxii
Parke, Davis and Company	ii, iii
Perkins School	xxvii
Pfizer Laboratories (Div. of Chas. Pfizer & Co., Inc.)	vi, xx
Ring Sanatorium	xxvii
A. H. Robins Company, Inc.	vii
J. B. Roerig Co.	viii
Royal Victoria Hospital	xxv
W. B. Saunders Company	Front Cover
Julius Schmid, Inc.	xxiii
G. D. Searle and Company	xix
Sharp & Dohme (Division of Merck & Co., Inc.)	xiv
Smith, Kline & French Laboratories	xxiv
E. R. Squibb & Sons (Division of Mathieson Chemical Corp.)	ix
Storrow House (Massachusetts General Hospital)	xxvi
United States Brewers Foundation, Inc.	xvii
The Upjohn Co.	v, xv, xxxiii
Washingtonian Hospital	xxvii
J. S. Waterman & Sons	xxv
Wine Advisory Board	xiii
Wiswall Sanatorium	xxvii
Woodside Cottages, Inc.	xxvii

(Concluded from page 372)

MONDAY, MARCH 14

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by Entire Surgical Staff and Anesthesia Staff. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m.–1:00 p.m. Therapeutic Conference. Dr. McCombs. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*4:00 p.m. Clinicopathological Conference. Pathology Conference Room, Beth Israel Hospital.
*4:00–5:00 p.m. Surgical Pathology. Dr. MacMahon. Stearns Auditorium, New England Center Hospital.
*4:00–5:30 p.m. Anesthesiology Conference. Preoperative Evaluation of Patient. Dr. Vandam. Peter Bent Brigham Hospital.
*5:00 p.m. Departments of Biological Chemistry and Physiology. Regulatory and Metabolic Obesities. Dr. Jean Mayer. Harvard Medical School, Bowditch Library, Building C, 25 Shattuck Street.
*5:00–6:30 p.m. Anesthesia Group of the Lahey Clinic. Joslin Auditorium, New England Deaconess Hospital.
*7:00–8:00 p.m. Pathology Conference. Dr. MacMahon and Staff. Stearns Auditorium, New England Center Hospital.
*7:00–9:00 p.m. Slide Seminar in Pathology. Dr. MacMahon. Stearns Auditorium, New England Center Hospital.
*8:30 p.m. Boston Surgical Society. Symposium on Original Research. Harvard Club, 374 Commonwealth Avenue.

TUESDAY, MARCH 15

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.
*10:30 a.m. More Than Sex Education. Mrs. Esther E. Sweeney. Lemuel Shattuck Hospital, 170 Morton Street, Jamaica Plain.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
12:00 m. South End Medical Club. Boston Tuberculosis Association. 554 Columbus Avenue.
*12:00 m. Pediatric Grand Rounds. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
*12:00 m.–1:00 p.m. Pediatric Grand Rounds. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
12:30–1:30 p.m. Medical Journal Club. Joslin Clinic. New England Deaconess Hospital.
*4:00–5:30 p.m. Anesthesia Conference. Dr. Etsten. Stearns Auditorium, New England Center Hospital.
*5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Service Meeting Followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.
*5:45 p.m. Mycotic Diseases of the Skin. Dr. Basil C. Gray. Joslin Auditorium, New England Deaconess Hospital.
*7:00 p.m. Some Aspects of the Pathogenesis of Atherosclerosis. Dr. David P. Barr. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
*8:00 p.m. Combined Rounds. Children's Hospital.

WEDNESDAY, MARCH 16

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00–10:00 a.m. Surgical Grand Rounds. Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Orthopedic Grand Rounds. Bigelow Amphitheater, White 3A, Massachusetts General Hospital.
*11:00 a.m. Boston State Hospital. Psychiatry Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Clinicopathological Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:00 m.–1:00 p.m. Roentgen Diagnostic Conference. 5th-floor teaching unit, Beth Israel Hospital.
*12:15 p.m. Vascular Rounds. Drs. Edward A. Edwards and Chilton Crane. D-Main, Peter Bent Brigham Hospital.
*12:30 p.m. Weekly Pathological Meeting. Joslin Auditorium, New England Deaconess Hospital.
12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. The Clinics of the Massachusetts General Hospital.
*2:00 p.m. Rectal Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*7:30–9:30 p.m. Lahey Clinic Lecture. Joslin Auditorium, New England Deaconess Hospital.

*Open to the medical profession.

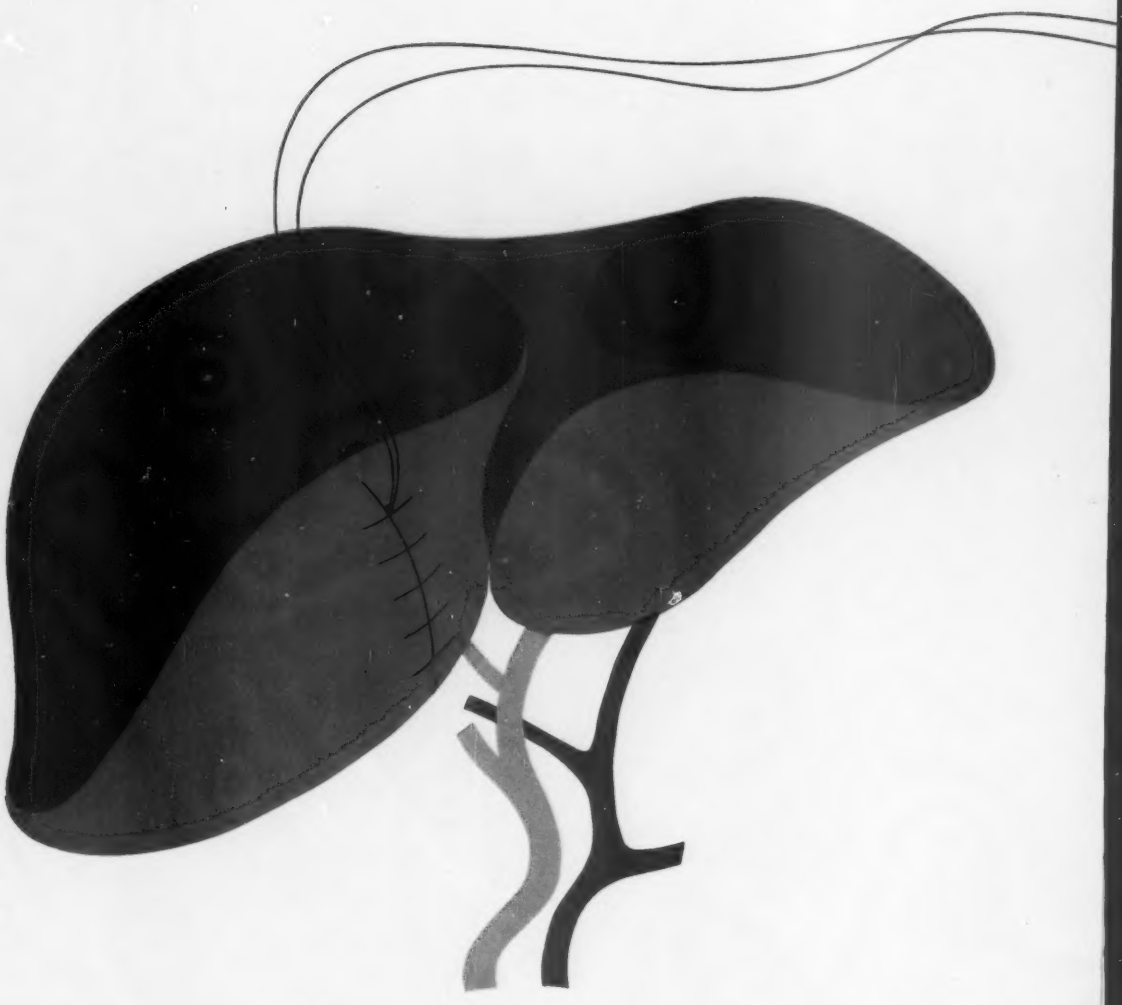
To prevent attacks and restore calm in Angina Pectoris

METAMINE, the new long-acting nitrate with the lowest dose and least side effects, is now available with butabarbital, widely accepted intermediate sedative. METAMINE *with* BUTABARBITAL prevents angina pectoris attacks and provides "therapeutic relaxation" to help the patient adjust to a level of activity within his limitations. DOSE: Swallow 1 tablet after each meal and 1 or 2 at bedtime. Vials of 50 tablets.

unique amino nitrate

NEW: **Metamine®** (2 MG.) **with**
triethanolamine trinitrate biphosphate, Leeming
Butabarbital (¼ GR.)

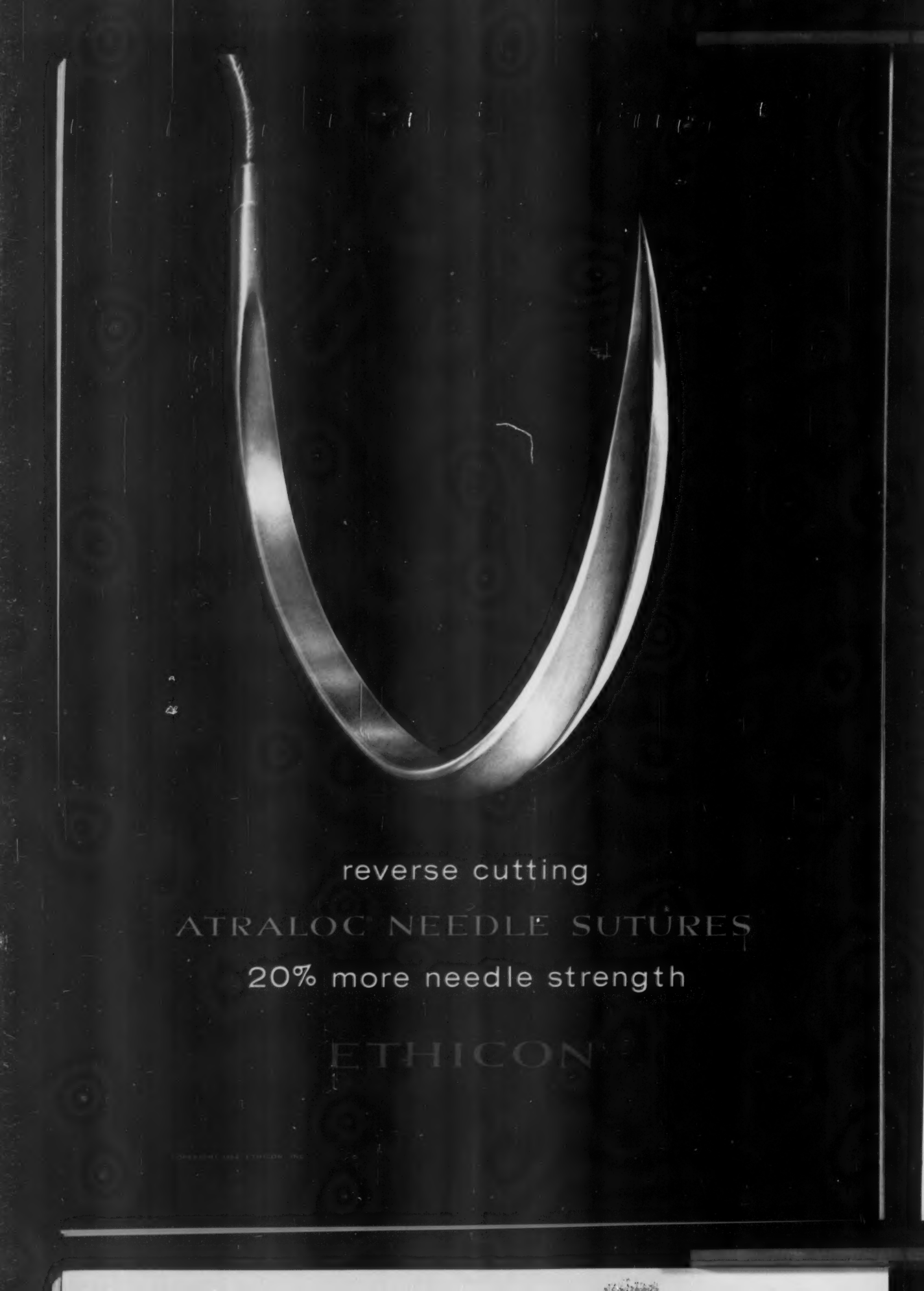
Thos. Leeming & Co. Inc. 155 E. 44th St., New York 17, N.Y.



setting new standards

ETHICON®

sutures


reverse cutting
ATRALOC NEEDLE SUTURES
20% more needle strength
ETHICON

IN TENSION AND HYPERTENSION

sedation without hypnosis

℞ Serpasil T. M.

(reserpine CIBA)

A pure crystalline alkaloid of rauwolfia root first identified, purified and introduced by CIBA

In anxiety, tension, nervousness and mild to severe neuroses—**as well as in hypertension**—SERPASIL provides a nonsoporific tranquilizing effect and a sense of well-being. Tablets, 0.25 mg. (scored) and 0.1 mg.

CIBA

SUMMIT, N. J.

3/2044M

TRIPLE SULFAS

Meth-Dia-Mer Sulfonamides

SULFADIAZINE SULFAMETHAZINE SULFAMERAZINE

unexcelled among sulfa drugs

for highest potency • wide spectrum
highest blood & tissue levels* • safety
minimal side effects • economy

Gram for gram, the Triple Sulfas produce and maintain higher blood and tissue levels with greater safety than any single sulfa. They are equally distinguished for their broad effectiveness and welcome economy.

These properties help explain why Triple Sulfas are by far the most widely used of all sulfas throughout the world, and why their use is increasing daily.

Triple Sulfas, alone or in combination with certain other agents, are available from leading pharmaceutical manufacturers under their own brand names. This message is presented in their behalf.

Cyanamid Fine Chemicals

Ask any medical representative about the Triple Sulfa products his company offers!

AMERICAN Cyanamid COMPANY, FINE CHEMICALS DIVISION, 30 ROCKEFELLER PLAZA, NEW YORK 20, N. Y.

whenever
cough
therapy
is indicated...

Hycodan

Bitartrate (Dihydrocodeinone Bitartrate)

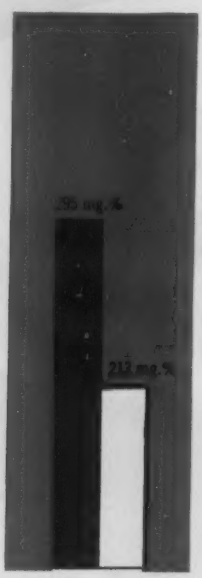
ACCEPTED COUNCIL ON PHARMACY AND CHEMISTRY MEDICAL ASSOCIATION

An AMA Council Accepted Cough Preparation

Syrup (5 mg. per teaspoonful), Oral Tablets (5 mg. per tablet).
May be habit-forming. Average adult dose, 5 mg. t.i.d. p.c.

Literature? write Endo®

ENDO PRODUCTS INC.,
Richmond Hill 18, New York



Supplied: Bottles of 12 fluid oz.
Literature available.

1. *Albert, A., and Albert, M.: Texas State J. Med. 50:814 (Dec.) 1954.*
2. *Sherber, D.A., and Levites, M.M.: J.A.M.A. 152:682 (June 20) 1953.*

Reduces elevated blood cholesterol levels.[1,2]

Improves hypercholesteremic patients with cardiovascular disease and angina and those with postoperative biliary dyskinesia, both subjectively and symptomatically.[1]

monichol*

Polysorbate 80, Choline, Inositol—the new physio-chemical complex)

normalizes cholesterol metabolism

IVES-CAMERON COMPANY

Philadelphia 2, Pa.

*Trademark

EMOTIONAL PROBLEMS
And What You Can Do About Them

FIRST AID TO WISER LIVING

By WILLIAM B. TERHUNE, M.D.

Medical Director, The Silver Hill Foundation, New Canaan, Conn.

The book that can be recommended to *anyone* with emotional difficulties . . . concise, practical, wise, dealing with the individual, his family, his friends, his children and his parents.

Dr. Winfred Overholser says: "I like Dr. Terhune's book. Unlike some of the recent non-medical publications of the Pollyanna variety, it recognizes that people do have problems, but at the same time presents possible and practical ways of meeting them. Dr. Terhune writes well and his writings spring from a large fund of psychiatric experience and of commonsense."

$3.00 at all bookstores, or from

WILLIAM MORROW AND COMPANY, INC.

425 Fourth Avenue, New York 16. (Please add 9¢ sales tax for delivery in N.Y.C.)

ELECTRON PHOTOMICROGRAPH

Hemophilus influenzae 64,000 X

Hemophilus influenzae ("influenza bacillus") is a Gram-negative organism which grows only in the presence of hemoglobin. Contrary to its name, it is not the causative agent in influenza, but rather is commonly involved in

meningitis • chronic bronchitis • bronchiolitis
tracheobronchitis • supraglottic laryngitis • bronchopneumonia

It is another of the more than 30 organisms susceptible to

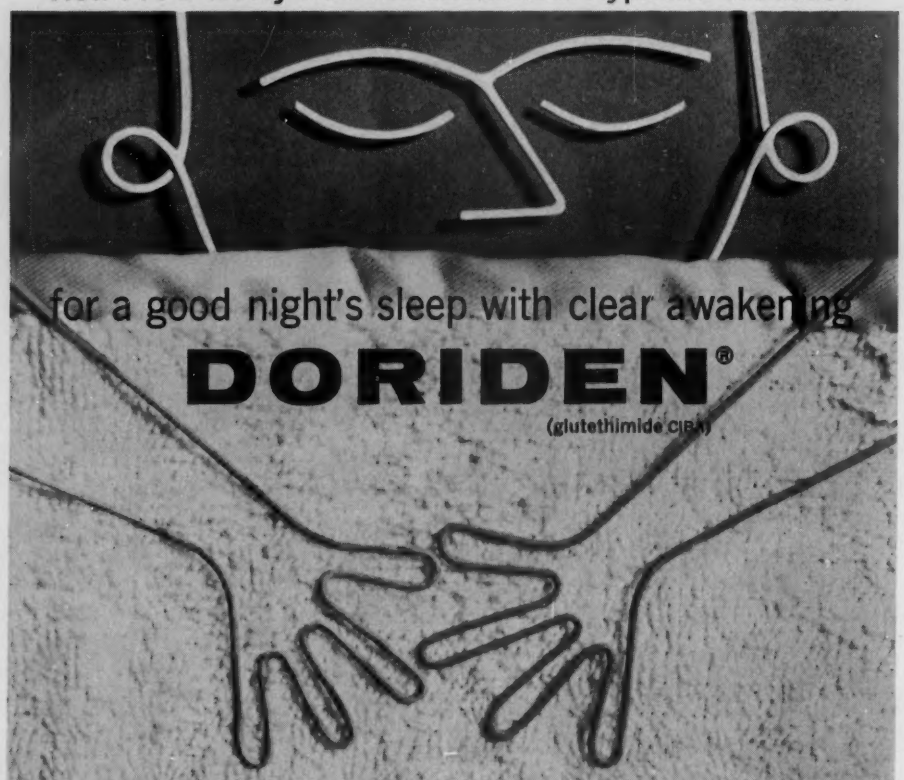
PANMYCIN* HCl

100 mg. and 250 mg. capsules
*125 mg./tsp. and 250 mg./tsp. oral suspension (**Panmycin** Readimixed)*

*TRADEMARK, REG. U.S. PAT. OFF.

Upjohn

Now . . . a totally new nonbarbiturate hypnotic-sedative!



for a good night's sleep with clear awakening

DORIDEN®

(glutethimide CIBA)

In most cases—

Rapid onset—15-20 minutes
Lasts 4-8 hours
No hangover

Dosage: 0.25 to 0.5 Gm. before bedtime.
Scored 0.25- and 0.5-Gm. tablets.

C I B A Summit, N. J.

2(20759)